JUL 1 8 1987

231-E-1

C 61.2: B52

BIOTECHNOLOGY IN WESTERN EUROPE

COMPLETED

U.S. DEPARTMENT OF COMMERCE
International Trade Administration

ORIGINAL

BIOTECHNOLOGY IN WESTERN EUROPE

Robert T. Yuan, Ph.D.

International Trade Administration
U.S. Department of Commerce
Washington, D.C.

April 1987

BLANK PAGE

FOREWORD

These reports on biotechnology in France; Federal Republic of Germany; Italy; the Netherlands; Norway, Finland and Denmark; Spain; Sweden; Switzerland; the United Kingdom; and the European Economic Community were prepared for the International Trade Administration, Department of Commerce, by Dr. Robert T. Yuan during his tenure as a Foreign Commercial Service Officer at the U.S. Embassy, London, United Kingdom.

Dr. Yuan currently is professor of microbiology at the University of Maryland at College Park, MD. He has extensive training in molecular biology. Prior to this assignment he taught at the Basel Biocentrum, Switzerland and Edinburgh University, Scotland. Additionally, he performed postdoctoral research at Harvard University. He is multilingual with significant knowledge of the culture and customs of many European and Asian peoples.

BLANK PAGE

TABLE OF CONTENTS

			Page
1.	Foreword		iii
2.	Introduction		1
3.	Executive Summary		3
4.	Biotechnology in France	Section A	25
5.	Biotechnology in Federal Republic of Germany	Section B	55
6.	Biotechnology in Italy	Section C	83
7.	Biotechnology in the Netherlands	Section D	100
8.	Biotechnology in Norway, Finland & Denmark	Section E	120
9.	Biotechnology in Spain	Section F	137
10.	Biotechnology in Sweden	Section G	156
11.	Biotechnology in Switzerland	Section H	181
12.	Biotechnology in the United Kingdom	Section I	204
13.	International Programs in Biotechnology in Western Europe	Section J	238
14.	Glossary	Section K	250

INTRODUCTION

This report is the result of a study carried out by the Biotechnology Program of the U.S. Department of Commerce. The Biotechnology Program is an experimental project of the International Trade Administration (ITA) and the U.S. and Foreign Commercial Service (US&FCS). It was established to carry out a technical and industrial assessment in the major industrial nations of Western Europe and the Far East. Its objectives are to:

- o determine the government policies in support of biotechnology,
- o identify the principal research laboratories and their activities,
- o identify the principal companies involved in biotechnology and their activities, and
- o study the various mechanisms for technology transfer from the research laboratories to the industrial sector.

In order to carry out this mission, two senior scientists were selected for posting to the U.S. Embassies in London and Tokyo. They were chosen on the basis of scientific expertise, work experience overseas, language proficiency, and the appropriate cultural affinities. Their efforts were coordinated through the ITA in Washington, D.C.

During the initial phase of this project, some 30 U.S. biotechnology companies were visited over a period of five months. This enabled the technical assessment officers to familiarize themselves with U.S. industry and its concerns. Contacts were made with the scientific attaches at the appropriate foreign embassies in Washington, to acquire information and names of individuals familiar with biotechnology in their respective countries. Once in London, lists of organizations and individuals involved in biotechnology in each country were obtained from three different sources: (a) colleagues in the scientific community, (b) the U.S. Embassy, and (c) officials of foreign governments. These lists were cross-checked against each other and against published articles and reports. A list of key individuals was generated and the appropriate U.S. Embassy made the necessary arrangements for a field trip. Usually, extensive reading and briefings took place prior to the actual interviews. The meetings also provided an opportunity to obtain further documents (frequently in the original language). Once the field visits to a given country were completed, the documents and notes were used in the preparation of a country report. Each of the country reports was reviewed by the U.S. Embassy FCS staff and knowledgeable individuals in that country. Their corrections and comments were incorporated prior to submission of the country reports to ITA in Washington.

The project in Western Europe had a duration of 16 months. It could not have been done without the enthusiastic cooperation of the U.S. missions abroad and of hosts of European officials, scientists, and corporate managers. It is inevitable that certain country reports are less thorough and complete than others, and there is the unfortunate omission of Belgium and Ireland. Such occurrences were not deliberate and must be understood in the context of problems with scheduling, logistics, and budgets.

This program was conceived and coordinated by Dr. Alfred Hellman, ITA, Washington, D.C. Mr. Michael Mercurio, Commercial Attache at the U.S. Embassy in London, provided invaluable support and Ms. Emily Arakaki, ITA, Washington, D.C., was a continuous source of information on the economics of biotechnology. The author is grateful for the assistance of Ms. Becky Roberts, US&FCS, U.S. Embassy, London, who provided invaluable research and editorial support. Finally, without the continuous support of Mr. Michael T. Kelley, Deputy Assistant Secretary for Basic Industries in ITA, Washington D.C., the program would not have been possible.

Unlike previous studies of this type, this one has both the advantages and disadvantages of having been done by one individual over a period of 16 months. As a senior scientist with extensive experience in Western Europe, he could deal with the same issues and make comparisons in country after country.

In addition to the country reports, the Biotechnology Program can count other accomplishments to its credit:

- o creation of a network of trade specialists knowledgeable about biotechnology at several of the U.S. Embassies in Europe,

- o provision of support for U.S. sponsored trade events in biotechnology, and

- o provision of information and assistance to U.S. biotechnology companies interested in operating in Western Europe.

The Biotechnology Program is an experiment in technology and industrial assessment. Unlike earlier studies, it was envisioned as a continuing effort based at the U.S. Embassies in London and Tokyo, and could be used as a model for similar programs in other high technology sectors. As such, the program deserves careful review and evaluation.

EXECUTIVE SUMMARY

A respected analyst of government policy and technology development remarked, in the course of a lengthy discussion, that certain factors are required for success in the development of high technology industries. They are: (1) a first-class science base or access to it, (2) an intelligent and supple management style, (3) sources of capital, and (4) a global strategy. "You Americans have an abundance of the first three," he pointed out. "It is on the fourth one that you lose out."

It is the objective of this study to provide an understanding of biotechnology in Western Europe. Each country report describes in some detail the national environment for biotechnology. Each is unique. This summary focuses on general characteristics and patterns, in particular, government policy, the science and industrial bases, and technology transfer. The last sections deal specifically with the U.S. competitive position and those issues relevant to an international strategy for U.S. biotechnology.

Biotechnology, as defined by the Office of Technology Assessment (OTA), is any technique that uses living organisms (or parts thereof) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses. For the purposes of this study, the focus is on the techniques of recombinant DNA, cell fusion and novel bioprocessing methods. The growth of biotechnology in Western Europe has coincided with national policies directed towards restructuring the economy away from traditional manufacturing and towards high technology sectors. Therefore, a great deal of what has been observed in biotechnology is probably also true for other rapidly developing high technologies such as computers and advanced materials.

Eleven countries in Western Europe are included in this study: the Netherlands, Norway, Finland, France, Germany, Switzerland, Spain, Italy, the United Kingdom, Denmark, and Sweden. Table 1 provides a brief summary of the principal characteristics of biotechnology in Western Europe.

I. GOVERNMENT POLICY

National governments and large established firms play the major roles in biotechnology in the absence of significant numbers of new biotechnology companies (except in the U.K. and Sweden). Table 2 summarizes the efforts of the European governments in support of biotechnology. The U.S. and Japan are included to provide a frame of reference. Government involvement has been divided into three separate categories: basic research, applied R&D and industrial activities.

Basic research is a major responsibility of the government in all countries studied. The most common form of government involvement is the funding of research carried out at universities. In addition, seven European countries and Japan have government research institutes, frequently organized into networks, such as the CNRS in France, the MRC in the United Kingdom (U.K.), and the Max Planck Society in West Germany. The closest U.S. equivalents are the National Institutes of Health (NIH) and certain biological programs in the National Laboratories.

Table 1.
CHARACTERISTICS OF BIOTECHNOLOGY IN WESTERN EUROPE

1. The basic research is world class in a number of key areas.

2. The R&D system provides few opportunities for independent research by young scientists and frequently fosters a negative attitude towards industrial activities.

3. The state plays an important, sometimes key role in industrial development.

4. Biotechnology is concentrated in large, established companies with long term R&D programs and strong cash reserves.

5. Venture capital is not readily available to new, small companies.

6. European companies are more likely to enter into partnerships with U.S. firms than with their European counterparts.

Table 2.
THE ROLE OF GOVERNMENT IN BIOTECHNOLOGY

	Basic Research		Applied R&D			Industrial Activity		
	Research Funding	Research Institutes	Technology Transfer Institutes	Funding		Tax Credits	Loans/ Grants	Risk Capital
				Univ/Inst	Industry			
Finland	+		+					
Norway	+	+						
Italy	+			+	+			
Spain	+	+	planned	+	+		+	+
Switzerland	+		+[1]	+/-[2]				
Denmark	+		+	+	+		+	
Sweden	+	+	+	+	+		+	+
Netherlands	+		+	+	+	+	+	+
France	+	+	+	+	+	+	+	
U.K.	+	+	+	+	+	+	+	+
Germany	+	+	+	+	+	+	+	+
Japan	+	+	+	+	+	+	+[3]	+
U.S.	+	NIH			+	+		

[1]Some activities at Swiss Federal Institute of Technology, Zurich
[2]Limited funding.
[3]Development banks/low interest

BEST COPY AVAILABLE

Support for universities is intrinsic to the health of the research establishment. In most governments, funding of universities is administered separately from that of basic research. So frequently, increases in research funding have gone hand in hand with massive cuts at the universities. This has resulted in a weakening of the scientific infrastructure and in projected shortages of skilled manpower.

The European university system has been slow in responding to the rapid growth of biological knowledge. One of the key concerns of university officials is the need for curriculum reform due to the interdisciplinary nature of biotechnology. This is compounded by the shortage of faculty positions which prevents the hiring of specialists in new fields, such as molecular immunology or plant molecular biology.

National biotechnology programs have been established in four countries and proposed in three others. Among them are two major countries (France and West Germany). In the U.K. and Japan, individual ministries and agencies have coordinated programs for biotechnology. Six countries have government involvement at all levels, from basic research to commercialization (Table 2). This is intended to speed up industrialization of new research findings. Government programs include, in applied R&D:

- o technology transfer institutes,
- o funding of applied R&D in universities, research institutes, and private companies;

and in industrial policy:

- o tax credits for industrial R&D and innovations,
- o loans and grants for new processes and products, and
- o risk capital for new companies.

In almost all countries, and particularly those with national programs in biotechnology, total actual funding has increased.

In addition to increases in funding support and changes in the structure of the research establishment, national programs also serve an important function in establishing a political consensus in support of biotechnology. Regional and local government can be an important element in the development of biotechnology. In most European countries, political and financial authority is highly centralized. In these countries, decentralization has become a major political issue, while in certain other countries (Switzerland, West Germany, and to a lesser degree, the Netherlands) provincial and local governments are responsible for the university system and its associated research establishments, as well as industrial development. Effective regional policy can play a pivotal role in technology transfer in such situations.

The pace of industrial development in biotechnology is set by government policy. The investment of industrial resources in a new technology such as biotechnology, depends on the overall environment in a specific country.

This is determined in large part by government policy on:

- o industrial participation in policy decisions,
- o support of R&D (particularly industry related),
- o fiscal measures,
- o tax and labor laws,
- o government pricing of both products and raw materials,
- o technology transfer,
- o government funding of new companies,
- o privatization of government-controlled companies, and
- o regulation of biotechnology.

The industrial sector (which is dominated by large companies) prefers indirect measures, such as the first five listed above. The government is concerned about the conservatism of industrial management, and active intervention is the rule rather than the exception (Table 2). National policy is limited by the ability of multinational companies to operate beyond national borders.

A major responsibility of government is the safety of new biotechnology products and processes. The lack of scientific knowledge about new genetically engineered organisms and their products, resulted in the imposition of strict research guidelines. No actual health hazard has emerged up to now, so the principal thrust of government policy is to support research on risk assessment, and use the results to develop safe procedures.

Restrictive legislation can sharply inhibit industrial applications of biotechnology. There has been serious concern about the potential risks associated with biotechnology which has led to the adoption of stringent regulations, such as those in Denmark (and proposed in West Germany). Such legislation can inhibit basic research and be an obstacle to industrial development in any country. The most rigorous legislation, however, can only have limited results if it disregards the general standards in existence in other countries. This has been a compelling argument for international cooperation to:

- o conduct rigorous scientific assessment of risks,
- o establish regulatory systems for research and industry, and
- o expand such regulations to less developed countries and those in the Eastern bloc.

The acquisition and dissemination of biotechnology information is a major function and one which could be a legitimate role of government. The extremely rapid pace of biological research has resulted in an exponential growth in information. This information can be purely scientific and/or commercial, for example:

- o DNA, RNA, and protein sequences,
- o structural data on biological molecules,
- o listings of microorganisms, plant and animal cell lines,

- o patent registration,
- o clinical trials, and
- o regulations.

Both individual countries (e.g., France and West Germany) and European organizations (European Molecular Biology Laboratory and the European Economic Community) have begun data projects. The most important of these is probably EBIP (European Biotechnology Information Project), a collaboration between the British Library and the European Economic Community (EEC). Information projects require technical expertise and timely dissemination. They also raise the issue of whether they are the proper function of the government or of autonomous non-profit institutions.

II. SCIENCE BASE

Taken as an aggregate, Europe has the second largest science base in biology and is moving to expand it. In looking at the science base, it is useful not only to look at the relative strengths of individual countries, but also at their performance in individual research areas. The research areas are the same ones used by the OTA in a 1984 study on "Commercial Biotechnology: An International Analysis":

- o pharmaceuticals (proteins, antibiotics, vaccines, diagnostics),
- o specialty chemicals and food additives (enzymes, sweeteners, amino acids),
- o agricultural (breeding of plants and animals, biological fertilizers and pesticides),
- o commodity chemicals and energy products (ethanol, solvents, mineral leaching),
- o environmental applications (treatment of solid and liquid wastes), and
- o bioelectronics (biosensors, biochips).

A summary of research and industrial activities in the U.S., Japan, and 11 countries in Western Europe appears in Table 3. These relate specifically to the novel technologies defined earlier. The country with the broadest spectrum of research activities is the U.K. (and Japan) followed by West Germany, the U.S., and the Netherlands. All countries, without exception, have focused on pharmaceuticals and human health care. There are much lower levels of research activity in agriculture, specialty chemicals, and food.

The major countries have programs to expand the breadth of their biological research. Some of the smaller countries have concentrated their efforts on subjects relevant to their own industry. U.S. research shows a pronounced bias towards the biomedical area.

Table 3.
BIOTECHNOLOGY ACTIVITIES IN WESTERN EUROPE

	Pharmaceuticals	Specialty Chemicals & Food Additives	Agriculturals	Commodity Chemicals & Energy Production	Environmental Applications	Bioelectronics
Finland	R/I	R/I	R*/I			
Norway	R	R	R			
Italy	R/I	R/I	R*			
Spain	R/I		R*			
Switzerland	R/I	R/I	R/I*			R*
Denmark	R/I	R/I	R			
Sweden	R/I	R/I	R/I		R/I*	R
Netherlands	R/I	R/I	R/I*		R/I	
France	R/I	R/I*	R			R*
U.K.	R/I	R/I	R/I	R	R/I*	R/I*
Germany	R/I	R/I	R		R	R
Japan	R/I	R/I	R/I	R/I*	R/I*	R/I*
U.S.	R/I	R/I	R/I		R*	R*

R=Basic Research
I=Industrial Activities
R*=Limited Activities
I*=Preliminary Activities

BEST COPY AVAILABLE

The rapid growth of the knowledge base will be limited by a number of "choke points." Modern biological research has developed, starting with bacterial and phage genetics, moving on to molecular and cell biology of simple organisms, proceeding to animal virology and, more recently, to molecular biology of plant and animal cells and novel fermentation and downstream processing technologies. The research activities of the principal laboratories in any given country have seldom been the result of conscious planning, but more often have been due to investigator initiative and peer review (determining government funding) and to the historical development of the laboratories. European governments and research organizations have become increasingly aware of the limited efforts being made in critical research areas. Certain ones are so important that they can limit the overall rate of biological research. These so-called "choke points" may vary somewhat from country to country, but there is surprising agreement on the following:

- o genetics and physiology of industrially relevant microorganisms (including industrial fermentation conditions),
- o enzymology (including use in production),
- o protein engineering,
- o genetics and physiology of plant and animal cells (including industrial fermentation conditions),
- o plant biochemistry,
- o use of microorganisms in bioconversion (including waste treatment),
- o use of enzymes and antibodies in biosensors,
- o risk assessment, and
- o bioreactor design, separation technology.

International cooperation is a potential solution to the problem of "choke points." Realistically, funding of research projects across national borders is rare, except in the context of the EEC and EUREKA programs. One of the most common mechanisms for expanding the science base of a given country is to send postdoctoral fellows and visiting scientists for training and research abroad. The most frequent host country is the U.S. The number of U.S. visiting scientists in European laboratories has decreased. This is considered to have had a negative effect on European science. It is also likely to have affected technology transfer from Europe to the U.S.

III. INDUSTRIAL BASE

Most analyses suggest that the first clients of biotechnological products and processes are likely to be industries. Industrial activities in biotechnology in Western Europe are to be found in large, diversified

multinationals (mainly in pharmaceuticals and chemicals), mid-sized multinationals (mainly in pharmaceuticals and specialty chemicals), and small new biotechnology companies (principally in contract R&D). Table 3 summarizes industrial activities in Western Europe, Japan and the U.S. Industrial activity (i.e., application of the new technologies) not only encompasses the manufacture of products and processes, but also contract R&D. As in basic research, the U.K. has the broadest spectrum of industrial activities (as does Japan) though their commercial success has been limited. There is a heavy emphasis on pharmaceuticals, followed at much lower levels by specialty chemicals and agriculturals.

The expansion and diversification of industrial activities has been promoted by government policy. This has usually been done by industrial innovation in established companies or, less frequently, by the creation of new companies. Table 3 shows that the impact of the new biotechnology programs on diversification has yet to be felt.

There is an important difference between the strength of the industrial base of a country and the strength of individual corporations based in that country. A number of small countries have major multinationals with well defined market niches, such as, Ciba-Geigy (Switzerland), and AKZO (Netherlands). These multinationals make the contribution of such countries to specific business sectors and their associated R&D very important.

The large multinationals are integrated, product-oriented, and endowed with extensive financial and technical resources. They have been generally conservative about biotechnology, but their acceptance of industrial innovation has made them purchasers of U.S. technology and companies. The mid-sized multinationals have specialized in biological processes and used them to develop global markets. Good examples are Pharmacia (separation technology), Novo (industrial enzymes), and Amersham (radioactive labeled compounds). The advent of the new biotechnology has provided them with new potential markets and the means to generate new products. The only European countries with significant numbers of new start-ups are the U.K., Sweden, and to a lesser degree, the Netherlands. The dynamics of such entrepreneurial firms requires them to move aggressively into new business sectors. Both small and medium-sized companies require industrial customers that are both profitable and compatible in technologies. When such partners cannot be found in the domestic environment, they must be sought abroad. The symbiotic relationship between small, new companies and large, established multinationals does not exist at present in Western Europe.

European companies are willing to take a long view, but usually along well defined product lines. At the same time, there is an increasing realization that they must acquire the technical capabilities now, in order not to be left behind in the future.

The widespread application of biotechnology to a variety of industries is also likely to encounter a number of "choke points." These can fall into the realms of science, government policy, and availability of capital. The

technical "choke points" have already been discussed in the preceding section. As regards government policy, the ones considered most critical are:

- o funding of basic research and training,
- o government pricing,
- o regulatory policy, and
- o tax and labor laws.

Availability of capital is often presented as a crucial "choke point" in the rapid development of biotechnology. In discussing this highly controversial issue, one must distinguish between the established, large multinationals and the struggling, small start-ups. An examination of the country reports will show that many of the large corporations are highly profitable and have amassed large cash reserves and/or raised additional capital, e.g., Glaxo (U.K.) had 1985 sales of $1.83 billion and profits of $345.7 million. Its cash reserves represent 40 percent of group assets. AKZO (the Netherlands) had 1984 sales of $5.15 billion and profits of $234 million, while accumulating an acquisition fund of $311 million. Capital is not a significant problem for such large multinationals.

Start-ups in Western Europe face obstacles in financing and in the business and cultural environments in which they operate. European governments have felt that the slow pace of industrial innovation is due to the limited number of small, new, high technology companies. The shortage of risk capital is viewed as one of the principal reasons for this situation. European entrepreneurs often find that they have to raise small amounts from a variety of sources (versus finding a small number of large investors as is the case in the U.S.) The amount of venture capital available in the EEC has been estimated at ECU 7 billion ($4.31 billion), which is quite a respectable sum, though considerably less than that available in the U.S. The U.K. has the largest share with 43 percent, followed by the Netherlands (18 percent), France (14 percent), and West Germany (9 percent). As important as the amount of venture capital, is the manner in which it is used. It has been observed that:

- o only half of the total venture capital is invested in small businesses,
- o over the period 1980-84, only 10 percent of the agreements involved foreign partners, and
- o good quality technology investments were more often found in the U.S. rather than in Europe.

These have been taken as indicators of the conservativeness of European venture capital organizations. In spite of this, more than half of the investments went into technology in general, and 4.5 percent into biotechnology specifically.

The business environment favors large established companies. A number of factors inhibit the formation of new companies:

- o tax structure (lack of incentives for investment in new, high technology firms),

- o labor laws and pension plans (discourage job mobility),
- o administrative costs and costs associated with raising capital in public markets are high,
- o pricing policies that favor established products,
- o access to distribution networks, and
- o differing technical standards from country to country.

The cultural environment is the most difficult to evaluate and to change, and is considered to encourage conservative attitudes. It includes:

- o favorable attitudes towards seniority and job security,
- o intrinsic respect towards large organizations and corporations,
- o high job prestige for university faculty and researchers, low for entrepreneurs,
- o high value is given to tangible assets, while new concepts and processes are considered of negligible value, and
- o failure has a negative connotation and no redeeming value as part of a learning process.

The limited number of independent positions for young scientists, and/or the length of the educational process, raises the average age at which scientists reach positions of responsibility. Though the variation in the structure of European research establishments is quite large, it is common that a scientist reaches an independent position with his own group in his late thirties or early forties. His American counterpart usually reaches his first independent position in his early thirties, and acquires a number of important skills, such as directing research, writing grant proposals, dealing with budgets, and managing a small group. Many of these skills are easily transposable to an industrial environment. If the acquisition of such skills occurs early, it is much more likely to lead to risk taking and an entrepreneurial attitude. Therefore, the combination of age and the seniority system are likely to have a profound effect on the pool of entrepreneurs.

A significant number of large and medium-sized European multinationals raise capital in foreign financial markets. This not only provides them with access to different sources of financing, but also gives them the flexibility to take advantage of different interest rates and changes in currency exchange rates.

IV. TECHNOLOGY TRANSFER

Technology transfer is the process by which the findings of research laboratories are introduced into the industrial sector and converted into new products. The principal mechanism of technology transfer in the U.S. is the

creation of new biotechnology companies. In Europe, it occurs internally within the large companies, or externally, through agreements and acquisitions.

Western Europe, in general, and the U.K. in particular, have experimented with more mechanisms of technology transfer than anyone else. Table 4 summarizes the mechanisms for technology transfer observed during the course of this study. It cannot be overemphasized that the success or failure of a specific form of technology transfer is a function of a given society and not necessarily applicable in a different country. Many mechanisms of technology transfer have been initiated only during the last 3 years, so any assessment of their effectiveness is premature.

Institutional mechanisms involve long-term commitments and large budgets. The justification for these is that certain types of R&D require an interdisciplinary approach and long-term funding. Government institutes include the network of TNO institutes (Netherlands) and the IBT and GBF (West Germany). In each case, focus has been on specific research problems (e.g., good processing, waste treatment) and development of joint projects with industry. The TNO institutes have a longer history and have been successful in establishing close ties to industry (they are partly dependent on R&D contracts), while the German institutes are more recent, and have been sharply criticized in terms of their science and their cost effectiveness. Swiss industry has invested heavily in private research institutes, such as the Miescher Institute (Ciba-Geigy) and the Roche Institute of Molecular Biology. Though such institutes have done first-class research, technology transfer to the industrial sector has been limited. The Battelle institutes in Frankfurt and Geneva are part of the U.S. not-for-profit organization that does contract R&D for government and industry. It is felt that in biotechnology, they are not competitive with the small biotechnology companies. Cambridge and Leicester universities (U.K.) have established biocenters in collaboration with private companies. The biocenters carry out research on topics of interest to those firms. Neither the biocenters, nor the science parks with an orientation towards biotechnology, have been in existence long enough to be evaluated.

Government support for applied R&D is an obvious extension of existing mechanisms for funding basic research. Most countries provide grants for applied R&D and technological innovation. There has been a growing emphasis on those projects involving university-industry interactions. The amount of funding is usually not large enough to influence the activities of the large companies. These grants do provide seed money for new projects, and are of particular importance to small new firms. Probably its single most important impact is to get academic researchers involved in industrial projects. Research clubs in the U.K. bring together university laboratories and companies that are interested in a specific research area (e.g., protein engineering). Government funds and corporate contributions are used to fund projects in that subject. Typical examples of joint ventures include the four companies formed by the Institut Pasteur (France) with private firms (e.g., Diagnostics Pasteur with the Sanofi company). Both research clubs and joint ventures are recent developments.

Table 4.

MECHANISMS OF TECHNOLOGY TRANSFER

1. Institutional
   a. Government institutes
   b. Private research institutes: corporate or independent
   c. University biocenters
   d. University science parks

2. Financial
   a. Grants for applied/generic research: industrial R&D
      university-industry R&D projects
   b. Grants for technological innovation
   c. Research clubs (government-industry)
   d. Joint ventures (research institute-industry)

3. Administrative
   a. University technology transfer office
   b. Graduate studentships in industry
   c. Consultantships in industry
   d. Temporary assignments from academia to industry and vice-versa
   e. Research round tables

4. Corporate
   a. Companies created by the government with special access to public research
   b. Public Corporation: licenses and invests in public research
   c. Establishment of new companies

5. Transnational R&D
   a. Contracts with new biotechnology companies (mainly U.S.)
   b. Funding of research in foreign laboratories (mainly U.S.)

Administrative arrangements have existed for a long time and provide a mechanism for individual involvement in technology transfer. New regulations allow students funded by government fellowships to do research in industry (CASE program in the U.K.). It has also been generally accepted that university faculty members can act as consultants for private firms. This practice is spreading to government research institutes. In addition, countries such as France and West Germany now allow academic researchers to be seconded to industrial laboratories and vice versa. It is not known whether this movement of personnel has actually increased, or even had much of an impact on, technology transfer. Universities have introduced technology transfer offices (e.g., University of Leiden in the Netherlands). These usually have dual functions: providing advice on patents and licenses, and acting as agents. It is felt that they provide a useful advisory function, but do not have the experience to be successful marketing arms. Research round tables (U.K.) are periodic, open discussions between scientists and industrialists on specific research topics. All of these measures are simple, relatively inexpensive, and foster university-industry interactions.

The establishment of new biotechnology companies is the most glamorous form of technology transfer, but is also expensive, complex, and very risky. The European dilemma is whether to leave this to the private sector or to have direct government involvement. The U.K. government has had the principal role in establishing several new biotechnology companies (e.g., Amersham, Celltech, and Agricultural Genetics Co.) in partnership with private investors. These new firms had, at the outset, access to the research from government-funded laboratories. As these firms became fully established, the government divested itself of its holdings. The British Technology Group is a public corporation that initially had rights of first refusal to all government-funded research. It functioned as an agent, provided funds for joint ventures, and was a source of venture capital. It has been more common for European governments to provide indirect support through loans and grants. Direct government support allows new companies to survive. Their commercial success depends on a combination of technical expertise and sound business management, plus compatible and wealthy large partners for production and marketing. There is scant evidence that direct government involvement is more effective than indirect measures in increasing the likelihood of success for new start-ups.

A variation on this theme is the effort of certain European countries to attract new U.S. biotechnology companies. If indigenous scientists are unwilling to establish new companies, the next best thing is to recruit foreign companies. The Netherlands now has four U.S. biotechnology companies. The U.K. has pursued a similar policy, and a number of U.S.-U.K. joint ventures now exist. France and Spain have also indicated an interest in this approach. For large, European multinationals, transnational R&D is the fastest and probably the most effective form of technology transfer. Table 5 has examples of the seven types of biotechnology contracts that have been observed between foreign and U.S. companies. Since the mechanisms for technology transfer in their own countries have been slow, and in many cases unproven, foreign corporations have used their extensive financial resources to enter into agreements with U.S. companies (particularly the small, new ones). As Figure 1 indicates, the numbers of such contracts has increased steadily in the period from 1981-86. These contracts were classified in the

manner shown in Table 5. Many of them included more than one type of agreement (e.g., a contract can cover agreements on both joint R&D and license/production). Table 6 shows a breakdown by type of agreement and by country. Japan is far ahead, with a total of 141 contracts, followed by the U.K. (35), West Germany (31), Switzerland (26), France (21), and Sweden (19). The total number of contracts for Western Europe is 173. The most common agreements with both Western Europe and Japan, are licenses for production and distribution/marketing. For the period under study, the significant difference between Europe and Japan is that the Japanese were not involved in acquisitions until 1986, while the Europeans started in 1981. The Japanese have made more use of contract R&D, reaching a peak of 11 contracts in 1982, and then dropping to 3 in 1985. This probably reflects the stronger science base in Europe at the beginning of this period, while the shift to joint R&D is probably an indicator of increased research capabilities abroad.

In addition, European multinationals have increased their funding of R&D in the U.S. As the competition for biotechnology products increases, many of the foreign multinationals have expanded their production and business operations in the U.S., which is frequently their single largest market. Traditionally, while multinational corporations have had their manufacturing and business operations all over the world, they have tended to retain their R&D operations in their home country. Now, in addition to their contracts with U.S. companies, there is every indication that R&D activities will also be located in the most advantageous environment. The U.S. represents one of the most appealing locations because of the size and quality of its research establishment, as well as its pool of scientific manpower. Table 7 shows a number of instances of R&D funding in the U.S. by European companies. This can take a number of different forms: funding of university departments/institutes (e.g., Hoechst), establishment of private research institutes (e.g., Roche), and acquisition of a company with its own research institute (e.g., AKZO). Most of these agreements were signed during the last 2 years. Frequently, the company gains access to basic research unavailable in its home country (e.g., Hoechst, AKZO) or increases the R&D capabilities in its major market (e.g., Alfa Laval).

Though European Governments have placed major emphasis on technology transfer, there is seldom a clear-cut definition of its objectives, nor milestones to measure its progress. Furthermore, in most cases, there is no mechanism for evaluating technology transfer.

V. INTERNATIONAL COMPETITIVENESS

In the preceding sections, biotechnology in Western Europe has been analyzed on its own terms. Here, it is compared with the situation in the U.S. The U.S. continues to have two strong advantages: its science base and its entrepreneurial, small, new companies. In addition, one cannot minimize the flexibility of its economic and political system that allows it to deal with rapid change.

The U.S. not only has a strong science base in biotechnology, but has been able to use that base to attract some of the best and the brightest in

Table 5.
EXAMPLES OF BIOTECHNOLOGY CONTRACTS

TYPE OF AGREEMENT	EXAMPLE
Acquisition	Organon Teknika, subsidiary of Akzo (Netherlands) acquired half of Litton Bionetics. Organon acquired the operations involved in R&D and manufacture of diagnostics, including the AIDS antibiodies test. (1985)
Venture Capital/ Equity Investment	Rothschild Inc. (U.K.) will provide Applied Biosystems $3.1 million in funding for the next two years. (1985)
Contract R&D	Genex agreed to perform contract R&D on behalf of Mitsui Toatsu Chemicals (Japan) to develop a microbial strain that produces human urokinase. Genex gets patent rights; Mitsui gets exclusive license for therapeutic uses for a 15-year period. (1982)
Joint R&D	Genentech and Speywood Laboratories (U.K.) agreed to cooperate in jointly developing Factor VIII. Genentech will have commercialization rights to the Western Hemisphere, Japan, and parts of Asia; Speywood in the rest of the world. (1982)
License/ Production	Ajinomoto (Japan) granted licensing rights for interleukin-2 to Hoffman-La Roche. Hoffman will have exclusive worldwide rights to produce the drug for sales, except for the Far East, in exchange for royalties on future sales. (1984)
License/ Distribution/ Marketing	Toray and Fuji Rebio (Japan) will distribute Centocor's monoclonal-based diagnostic cancer tests. (1985)
Joint Production/ Marketing/Distrib./ Establishment of New Firm	Pharmacia (Sweden) and Chiron have agreed to form a 50/50 joint venture to commercialize super oxide dismutase (SOD). Chiron will contribute its production technology; Pharmacia will contribute regulatory and other premarketing assistance and funding. Chiron retains rights to manufacture SOD, which will be distributed by Pharmacia. (1985)

Table 6.
INTERNATIONAL BIOTECHNOLOGY AGREEMENTS
1981-1st Quarter of 1986

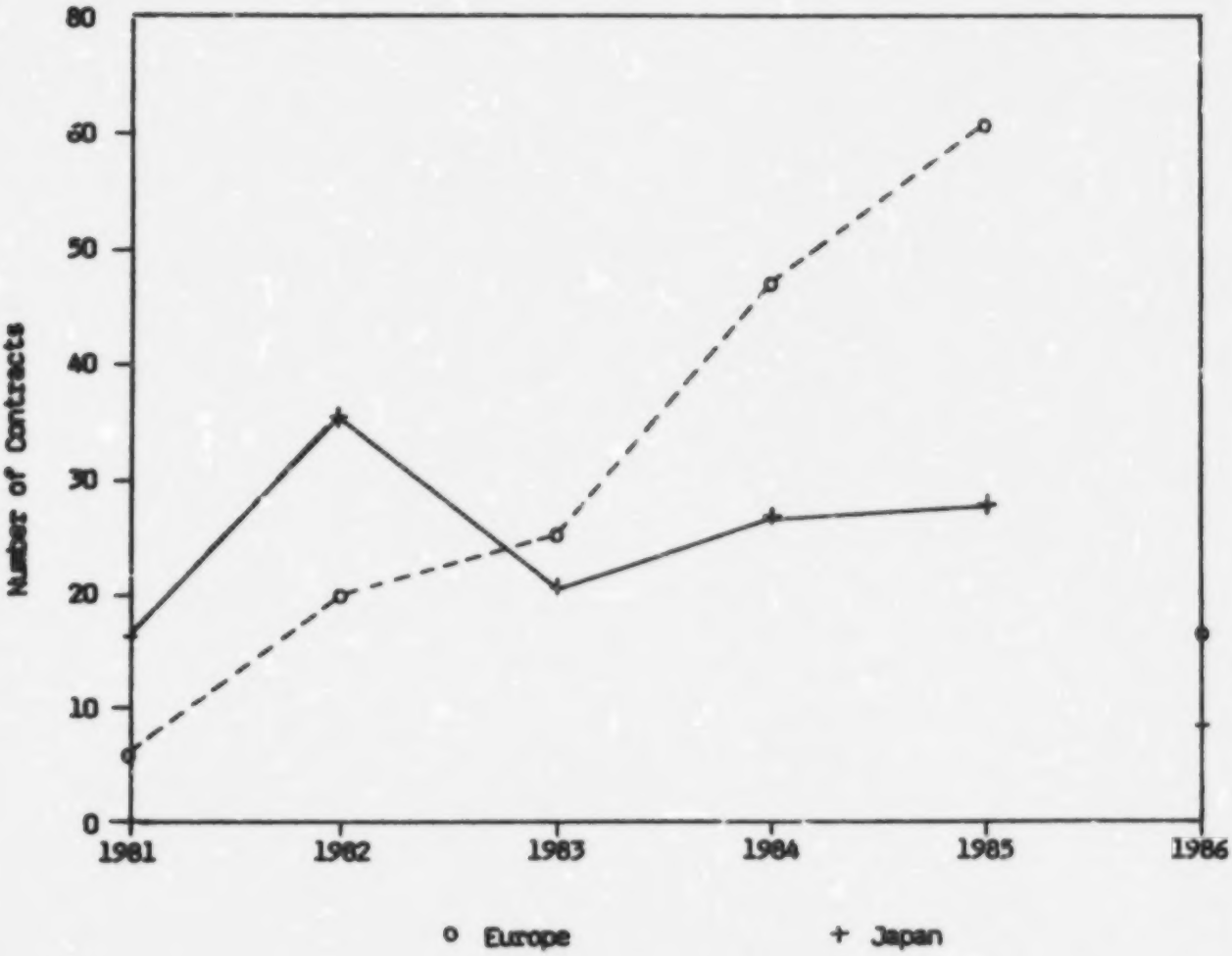
	Acquisition	Venture Capital/ Equity Investment	Contract R&D	Joint R&D	License/Production	Distribution/Marketing	Joint Production/Marketing Distrib./Estab. of New Firm	Total Types of Agreements*	Total Number of Contracts
Belgium	1	1	1	3		1	2	9	9
Denmark		1	2	2	1	1	1	8	7
Finland			1		1	3		5	3
France	4	1	6	3	4	6	5	29	21
Germany	1	1	7	6	14	18	3	50	31
Italy		3	1	3	2	1	1	11	10
Netherlands	2	3		2		2	1	10	9
Norway		1						1	1
Spain		1		1			1	3	2
Sweden	3	3	5	3	5	6	3	25	19
Switzerland	1	2	11	4	5	6	5	34	26
U.K.	4	11	4	5	4	5	5	38	35
Total Europe	16	28	38	33	36	49	27	227	173
Japan	2	24	30	24	40	59	24	203	141

Note: This table is based on data compiled by Rachel Schiller, Office of Basic Industries, International Trade Administration, U.S. Department of Commerce.

*Some contracts may involve more than one type of agreement.

BEST COPY AVAILABLE

Figure 1.
INTERNATIONAL BIOTECHNOLOGY AGREEMENTS
(1981-1st Quarter 1986)



	1981	1982	1983	1984	1985	1986(1)	Total
Europe	6	22	26	41	61	17	173
Japan	16	36	23	28	29	9	141

Note: This figure is based on data compiled by Rachel Schiller, Office of Basic Industries, International Trade Administration, U.S. Department of Commerce.

BEST COPY AVAILABLE

BLANK PAGE

Table 7.
FUNDING OF R&D IN THE U.S. BY EUROPEAN COMPANIES

European Company	U.S. Institution	Funding Mechanism	Cost	R&D Area
Hoechst (FRG) 1981	Massachusetts General Hospital	Research grant to Dept. of Genetics	$50M/10 yrs	Plant molecular biology
Alfa-Laval (Sweden) 1985	Massachusetts Institute of Technology (MIT)	Equipment of Dept. of Biochemical Engineering	$1M	Fermentation & downstream processing
FIDIA (Italy) 1985	Georgetown University	Funding of new research institute	$3M/yr for twenty years	Neurophysiology
Roche (Switzerland) 1969	Institute of Molecular Biology	Funding of industrial research institute	$15M/yr	Molecular & cell biology
Glaxo (U.K.) 1986	Glaxo Research Institute	Funding of industrial research institute	$9M	Pharmaceutical
AKZO (Netherlands) 1985	Litton Institute of Advanced Biotechnology	Acquisition of industrial research institute	$59M	Cancer diagnosis & therapy

the international scientific community. The science base is vulnerable in that there is heavy emphasis on the biomedical sector and low levels of activity in some of the "choke points" identified in the science base section. Technology transfer has too often been viewed as a one-way street, going from the U.S. to foreign countries. This NIH (Not Invented Here) Syndrome ignores the excellence of much European research, particularly in specific areas such as plant molecular biology, enzymology, and biosensors. The sharp decrease in the number of American visiting scientists in European laboratories will have a negative effect, not only in learning about developments there, but also in establishing the personal networks that are such a crucial element in collaboration and information exchange.

The U.S. has the strongest industrial base, but its spectrum of biotechnology activities should be widened, particularly into such key sectors as specialty chemicals, waste treatment and bioelectronics. It is generally felt that the major economic impact of biotechnology will be its application to a wide range of industries. The emphasis on a rapid return on investment has caused U.S. industry to focus on the biomedical sector. Nevertheless, the U.S. has a healthy mix of small, medium-sized, and large companies that can make effective use of the new technologies.

The principal mechanism for technology transfer in the U.S. is the formation of new, small biotechnology companies. Alternative mechanisms should be explored. It is likely that their implementation will occur at the State and local levels (e.g., university biocenters) and that it will involve novel (for the U.S.) forms of federal government-state/local government-university-industry collaboration. Close attention should be paid to current efforts on technology transfer in Europe.

American laboratories, government agencies, and private companies are less likely to develop global strategies than their European counterparts. In order to maintain a competitive edge, there is a need for:

- o increased awareness of basic research conducted in the principal European laboratories,
- o more information about the activities of European companies,
- o detailed analyses of national markets in biotechnology, and
- o better integration of domestic and international business strategy.

The U.S. educational system does not adequately prepare its graduates for an increasingly global environment. At the scientific level, there is little effort to familiarize students with research done abroad, nor does it encourage them to do research outside the U.S. On a more general level, education in foreign languages, European geography and culture, is limited.

Career development in the U.S. does not normally include, and seldom rewards, work experience in Western Europe. In basic research, investigators who have spent any extended period in a European laboratory, find reentry into

the American research establishment difficult. In many corporations, overseas assignments are outside the regular career track. This is in sharp contrast to most European countries, where an overseas assignment is highly desirable, if not essential for promotion to high responsibility. Immersion in a European environment sensitizes the individual to those national characteristics that make him more effective in the pursuit of scientific, political, or commercial goals. An examination of individual country reports will show that biotechnology in each nation reflects its culture and institutions. European societies are more complex, and a great deal of power is in the hands of small elites. To be effective in such an environment requires developing good personal relationships. This requires a larger investment of time and effort than in the U.S. On the other hand, greater job security, and lower labor mobility, is likely to make such relationships much more rewarding in the long-term.

ISSUES

The industrial development of biotechnology in the U.S. has progressed at a rapid pace, and the U.S. is in a favored position. Its principal trading partners have developed policies to become increasingly competitive. The U.S. must be conscious of the need for a more concerted effort involving government, universities and industry. In addition, it cannot be overemphasized that such efforts are generally applicable to other high technology sectors. The principal issues identified in this study are:

BASIC RESEARCH

- A need for stable, long-term funding
- A reevaluation of the present funding system, with particular emphasis on interdisciplinary research and the support of young investigators
- A need for rebuilding and maintaining the scientific infrastructure of the universities
- An assessment of potential scientific "choke points" and increasing research in those areas
- Increasing collaboration and visiting appointments with European laboratories
- Collaborating with the EEC on risk assessment
- Assessment of the need for applied R&D and development of joint university-industry efforts
- Concerted government-industry efforts in dealing with "choke points" relating to economic and political issues

UNIVERSITIES

- Universities not only have a role in research and education, but also in technology transfer. They, along with state governments, should develop their capabilities in that direction.

- University training should place greater emphasis on presenting subjects in a more international context.

LONG RANGE TECHNOLOGY POLICY

- Federal government should assist state governments in developing technology-directed development policies.

- A federal agency should have the key role in acquisition and evaluation of information relating to high technology in foreign countries.

- International competitiveness should be an intrinsic aspect of all government policy relating to science and technology.

ROLES OF PUBLIC AND PRIVATE ORGANIZATIONS

- In all countries, there is serious doubt of the effectiveness of a single government agency acting as banker, manager, agent, and reviewer. It has been suggested that assessment and evaluation of science and technology policy should be the responsibility of autonomous, non-profit organizations.

SECTION A

BIOTECHNOLOGY IN FRANCE

SUMMARY

The involvement of the French government in biotechnology is ubiquitous at all levels. In recognition of the strategic importance of biotechnology, the government established a "Mobilization Program for the Development of Biotechnologies" in 1982. Severe problems with the economy prevented its full implementation. The "Draft Law of 1986" was intended to make a more realistic effort with the resources available.

In research, there are clear indications that basic research in biology had been allowed to languish. The Mobilization Program was intended to strengthen the science base and promote higher levels of activity in all research areas. Its impact has been most marked in rebuilding the scientific infrastructure and in building up major research centers outside of Paris in Strasbourg, Toulouse and Compiegne. However, even if more extensive funding were available, it is questionable whether it could be used effectively in the absence of a better integration of research efforts in government institutes and universities.

French industry has always had a conservative attitude towards R&D, and biotechnology has not been an exception. Three of the major corporate groups are moving to expand their R&D efforts. One of their major concerns is increasing competition in both the domestic and international markets. A number of small biotechnology companies have been started with government support, and there is a major effort to improve collaboration between industrial laboratories and public research institutes. However, it is acknowledged that this will be a slow process.

The election of a conservative government in March 1986, is likely to have a direct effect on the Mobilization Program, both by reducing the budgets for R&D, and by a reorganization of the government agencies involved in science and technology policy. It is feared that this will make it even more difficult for France to remain competitive in this field.

French biotechnology suffers from a state of self-imposed isolation. French scientists still do not spend extensive periods abroad, few technical managers have international experience, and significant numbers of senior government officials and corporate managers are only fluent in French. In the key pharmaceutical and agro-food industries, French companies have been slow to develop foreign markets, particularly in the all-important North American and Japanese ones.

I. INTRODUCTION

France is one of the major countries in Western Europe. During the past few years, its economy has been characterized by slow growth, inadequate industrial investment, and a high unemployment rate of around 11 percent. The

decline of traditional manufacturing was in sharp contrast to the rapid growth of new high technology industries in the U.S. This decline led to a policy of restructuring manufacturing industries along with an attempt to expand R&D activities in new technologies. With the election of the Socialist government in 1981, this policy was pursued even more aggressively, with a stated goal of having R&D expenditures rise to a level of 2.5 percent of GNP (1). The government also developed a series of "mobilization programs" in strategic industries. The Mobilization Program for Biotechnology was unveiled in 1982, with the stated goal of having 10 percent of the world biotechnology market by 1990 (2). The French government committed itself to invest FFr 1.1 billion ($122.4 million)* in biotechnology R&D, from 1983-85. Following severe economic difficulties, that amount was severely reduced. It is now estimated that only FFr 95 million ($10.6 million) were actually spent during that period (2).

To a degree unmatched in other Western countries, the French government dominates biotechnology activities at all levels. It funds basic research; it is an owner or stockholder in the major industrial users of the new technologies, (e.g., Elf-Aquitaine is 67 percent state owned); it controls key banking and financial institutions (e.g., Paribas is nationalized); and it influences consumption of new products (e.g., health care is socialized, prices and procurement policies can be set by the state). This strategy may be partially modified with the recent election of a conservative government committed to a reduction in government expenditures and to privatization.

France launched its biotechnology program with the full realization that it started from a weak position. Its basic research establishment had suffered from years of neglect and potential industrial users of the new technologies had a poor record of commitment to R&D and technological innovation.

II. GOVERNMENT POLICY

Mobilization Program in Biotechnology (Original Version)

The fundamental document for this French program was published in 1982 under the aegis of a National Committee presided over by the Minister of Industry and Research. One of its most valuable contributions was an assessment of France's position in biotechnology. Initially, the committee divided the field into three parts: basic research, application of the full range of new biological techniques (called "the biotechnologies" by the French), and fermentation and downstream processing. While the first two areas were covered by one or more of the public research organizations, there was very little being done in the very important third area.

An initial cross-listing of technologies, industrial applications, and research institutions resulted in Table 1, which showed serious weaknesses.

*Average exchange rate for 1985: French francs (FFr) 8.9852 = $1.

Table 1.
BASIC RESEARCH - MAJOR ORGANIZATIONS & UNIVERSITIES

Centers of development: Pasteur Institute, INRA[1], INSERM[2], CNRS[3], Universities

	Pharmaceuticals	Reagents	Agro-Food Products	Raw Materials Chemicals Energy	Biodegradation & Environment
Genetic Engineering	CNRS INRA Pasteur Institute INSERM	INSERM Universities ENV	INRA (Versailles) INA	CEA	
Cell Fusion	Pasteur Institute INSERM Universities	INSERM Universities Pasteur Institute	INRA Universities		
Enzymes & Enzyme Engineering	Pasteur Institute Universities CNRS	Universities	Universities INRA ENV	Universities IFP INRA	Universities IFREMER INRA
Fermentation & Tissue Culture	Pasteur Institute Universities	Universities CNRS INSERM	Universities INRA ORSTROM-IRCHA	Universities IFP CNRS	
Instrumentation & Downstream Processing		Universities	Universities IFP IRCHA	Universities CNRS IFP CEA	Universities
Strain Collections & Data Banks	Pasteur Institute Universities CNRS	Universities CNRS	INRA Museum		

Source:translated from the "Mobilization Program" document, 1982.
1 Institut National de la Recherche Agronomique (National Institute of Agronomic Research)
2 Institut National de la Sante et de la Recherche Medicale (National Institute of Health and Medical Research)
3 Centre National de la Recherche Scientifique (National Center of Scientific Research)
ENV=ECole Nationale Veterinaire
INA=Institut National Agronomique
ORSTROM=Institut Francais de Recherche Scientifique pour le Developpement en Cooperation
IRCHA=Institut National de la Recherche Chimique Appliquee
IFP=Institut Francais du Petrole
IFREMER=Institut Francais de Recherche pour l'Exploitation de la Mer

Upon more careful inspection, the number and quality of research groups was deemed to be unsatisfactory in a number of areas:

- o bacterial genetics,
- o basic and industrial microbiology,
- o plant molecular biology,
- o fermentation and downstream processing, and
- o animal and plant tissue culture.

Furthermore, the new techniques of recombinant DNA (rDNA), hybridomas, and protein modification and isolation were not being widely disseminated even within research institutes. It was ascertained that many of the laboratories were not even appropriately equipped to carry out such necessary work.

A parallel cross-listing of industries using biotechnology was done (Table 2). The picture that emerged was, if anything, even more depressing. The total number of companies was very small. In comparison to the U.S. where each block would contain the names of 20-60 companies, here there was only a handful. Even more seriously, the use of the new technologies was very limited. The situation was even more dramatic if one looked at specific markets. The French diagnostics market has sales of FFr 1.3 billion ($144.7 million). French products account for 38 percent of this amount, but for only 4 percent of the reagents that go into them (2). The low level of investment in biological R&D not only prevents a competitive position in the global market, but leaves the domestic market open to foreign domination. The Mobilization Program was an attempt to address all of these issues, but a downturn in the economy prevented its total implementation. Looking back to 1985, Dr. Gilbert Durand, former director of the Program, felt that it had suffered less from a shortage of funds than from inadequate research in certain sectors, lack of flexibility in the research organizations, and reluctance of industry to invest in R&D.

Mobilization Program (version 2, 1986)

The end of the first 3-year period led to a reassessment of the program which was incorporated into the budget proposal for 1986. The overall situation was considered to be favorable. The strengths in the biological sciences were outlined once more: neurosciences, cellular immunology, developmental biology, control of gene expression. An analysis of publications was used as proof that France competed with West Germany for third place after the U.S. and the U.K. except in the areas of instrumentation and industrial applications. It was generally felt that there had been significant progress in restructuring French basic research through:

(1) reorganization of research institutions and increase in technology transfer,

(2) establishment of new research priorities in existing organizations,

Table 2.
INDUSTRIAL RESEARCH

Three Key Centers of Development: Rhone-Poulenc, SNEA (of Sanofi), Roussel-Uclaf

	Pharmaceuticals	Reagents	Agro-Food Products	Raw Materials Chemicals Energy	Biodegradation & Environment
Genetic Engineering	G3 *Transgene *Genetica *Roussel-Uclaf *Pharmuka	*Intergene	*Agrigene (Transgene) *Roussel-Uclaf *SNEA *BSN		
Cell Fusion	Rhone-Poulenc	*Immunotech *Hybridolab (Pasteur I.) *Clonetech	Clause *SNEA Limagrain		
Enzymes & Enzyme Engineering	Rhone-Poulenc	Biotechnika Biosys	Roquette		
Fermentation & Tissue Culture	*Roussel-Uclaf Rhone-Poulenc *Sanofi Merieux Synthe-Labo		Lafarge-Coppee Bel, Bongrain Sodima *Rhone-Poulenc *Protex Pernod-Ricard Air Liquide	EMC Rhone-Poulenc	
Instrumentation & Downstream Processing	Rhone-Poulenc Biolafitte	Biosys	Biolafitte Nordon Setric Technip (IFP) Speichim BSN		Degremont (Lyonnaise des Eaux) Compagnie Generale des Eaux
Strain Collections & Data Banks	Pasteur Institute		*Museum		

*Companies that have applied for government subsidies for R&D.

(3) establishment of new facilities (e.g. Plant Molecular Biology Institute in Strasbourg), and

(4) establishment of needed infrastructure (e.g. nucleic acid data banks at the Pasteur Institute, and in Strasbourg).

The weaknesses in research sectors highlighted earlier (e.g., downstream processing) were still there as well as the problems of getting widespread use of the new technologies in both government and industrial laboratories. In the research organizations, there were still serious infrastructure problems such as:

- o the foreign origin of most basic reagents and laboratory equipment,
- o computer needs,
- o laboratory modernization, and
- o capital equipment.

In the industrial sector, it was too early to judge the impact of the new industrial incentive programs. However, there was still dissatisfaction with the use of the new technologies by industry. For example, the pharmaceutical and agro-food industries are large and important parts of the French economy. The French pharmaceutical industry is third in export sales, but it lags far behind in R&D expenditures [in billions of FFr: U.S., 19.3; Japan, 7.3; Germany, 7.0; U.K., 6.0; France, 4.3 (3)]. The agro-food industry only invests about 0.2 percent of its sales in R&D (4).

In 1983-84, the sum of FFr 80 million/year ($8.9 million) was spent on the Mobilization Program, of which 80 percent was allocated in the following manner (5):

- o 10 percent for training, and establishment of data banks and microbial strain collections;
- o 25 percent for public research agencies;
- o 10 percent for multidisciplinary research projects involving public and private organizations; and
- o 55 percent for incentive research contracts with companies (priority to the agro-food industry).

The remainder was used for discretionary purposes (5). The program itself was reorganized and now consists of the following committees:

(1) Program Committee: responsible for policy and headed by Professor P. Douzou with the assistance of Professor F. Gros (former adviser to the Prime Minister), plus 5 members of the Administration, 6 members from public research agencies and 10 representatives from companies.

(2) Directorate for Projects: responsible for implementation of policies under the direction of Professor D. Thomas. The Directorate will be advised by three scientific committees: (a) Computer Science and Biotechnology, (b) Health, and (c) Microbiology and Enzyme Technology. The need for a fourth committee on Plant Genetics is presently being discussed.

BASIC RESEARCH

In sharp contrast to most industrialized nations, the majority of basic research in France is carried out by government research agencies. Many of their groups are located in the French universities. [The total budget for university research in all areas is only FFr 1 billion/year ($111.3 million)] (1). The Mobilization Program has a budget of FFr 110 million ($12.24 million) for 1986 (3). Table 3 summarizes the budgets, staffs, and activities of the principal research agencies. These are administered through the Ministry of Research and Technology and funded, in part, from its budget. In addition, a number of other ministries/agencies have small programs in biotechnology. The Atomic Energy Agency (CEA) carries out research in radiobiology, instrumentation and analytical procedures, and downstream processing. The Ministry of Education has primary responsibility for training and is developing research-oriented engineering programs. The Ministry for Cooperation and Development funds a number of cooperative research projects with lesser developed countries in the areas of public health and agronomy.

DIRECT SUPPORT FOR INDUSTRIAL RESEARCH

National Agency for Commercialization of Research (ANVAR) was established in 1968 for the express purpose of identifying fundamental research that could lead to industrial applications. In 1979, it was assigned the additional responsibility to stimulate innovation. Government programs can provide loans and subsidies that can cover a maximum of 50 percent of research programs.

ANVAR was allocated some FFr 11 billion ($1.22 billion) in 1984, with a similar amount for 1985 (3). These funds were invested through two programs:

(1) Program for Innovation provides loans for the final development of a product or process prior to final commercialization. In 1984, the available credits totalled FFr 899.6 million ($100 million) of which FFr 866.8 million ($96.5 million) were used to fund 2,203 applications (3). Almost two-thirds of the recipients were small or medium-sized companies.

(2) Industrial Fund for Modernization (FIM) provides 5-10 year loans for the purchase and installation of new industrial equipment. One thousand fifty-three applications were funded for a total of FFr 9.265 billion ($1.03 billion) (3). A considerable proportion of these loans went for computer and electronic equipment, as well as for modern production equipment. Approximately the same amount was to have been spent in 1985.

Table 3.
FRENCH GOVERNMENT RESEARCH AGENCIES
INVOLVED IN BIOTECHNOLOGY

	CNRS[1]	INSERM[2]	INRA[3]	Pasteur Institute
Number of staff	600 scientists 700 associate scientists 700 technicians	220 scientists 170 associate scientists 500 technicians	8000 (1400 scientists)	400 scientists 200 associate scientists 1000 technicians
Total Budget	$38M	$14M	$20M	$6.3M
Operating costs*	$9M	$6M	$3.1M	$4.5M
Research Priorities	Gene expression Molecular genetics & nervous system Molecular genetics & endocrinology Genetic probes & human disease Applications of biotechnology	Molecular biology w/emphasis on eukaryotes Cell biology Immunology Biochemical signals & receptors Medical applications	Soil microbiology Animal health care Plant molecular biology, physiology & biochemistry Enzymes & fermentation technology	Molecular biology of bacteria & their viruses Eukaryotic molecular biology (development) Immunology; vaccines Virology Applications of genetic engineering

*exclusive of salary
1 Centre National de la Recherche Scientifique (National Center of Scientific Research)
2 Institut National de la Sante et de la Recherche Medicale (National Institute of Health and Medical Research)
3 Institut National de la Recherche Agronomique (National Institute of Agronomic Research)
M= millions

In 1985, ANVAR's two primary goals were: (1) simplification of procedures, and (2) increased support for innovation. During 1986, it will concentrate on the creation of new companies through the following mechanisms:

- o creation of a loan service for new technologically oriented companies,
- o creation of a multi-agency project to provide information and advice to researchers interested in creating new companies,
- o establishment of a program whereby academic researchers can be seconded to ANVAR during the start-up phase of a company, and
- o leave status for investigators (up to 75 percent of their time) involved in the creation of a new company.

One important feature of ANVAR is the decentralization of its operations and its establishment of a network of local offices throughout France. The new government has reduced ANVAR's budget by FFr 400 million ($44.5 million) (8). ANVAR has been strongly criticized for what is considered to be excessive administrative costs and for its financing of large companies that can readily support their own new programs.

INDIRECT SUPPORT FOR INDUSTRIAL RESEARCH

Since French industry has a poor record of investment in R&D, the government has established a number of programs to stimulate such activities.

R&D Tax Credit covers 25 percent of the annual increase in R&D. It is estimated that in 1985, approximately 2,000 companies applied for it, and that the cost to the government would be around FFr 420 million ($46.7 million). The budget estimates for 1986 are for FFr 1.04 billion ($115.7 million). Analysis suggests that this credit goes primarily to the most dynamic companies (those with an average increase in R&D of 9 percent). Sixty-one percent of the applicants were small firms with less than 500 employees and received about 30 percent of the credits. The costs eligible for the credit are: depreciation of fixed assets (exclusive of buildings), personnel expenses for R&D, operational expenses, contract research, and the costs of obtaining patents (3).

Finance Companies for Innovation (SFI) were created in 1972 for the industrialization of technological research as well as the promotion and exploitation of inventions leading to new products, methods or techniques. They have these advantages: special depreciation of 75 percent for investments in R&D, and no VAT (value added tax) on stock transfer within the limits of the special depreciation. They are required to: (1) have a minimum capital of FFr 10 million ($1.11 million), (2) invest 80 percent of their capital in innovative companies, (3) invest not more than 25 percent in any one company, (4) renew their investments every 3 years, and (5) divest themselves of 33 percent of the capital held more than 5 years. There are now 13 SFI's with a total capital of FFr 620 million ($69 million) (3).

Mutual Funds for Risk Capital numbered some 40 in 1984, with a total capital of FFr 655 million ($72.9 million). Investors in such funds do not have to pay income tax or VAT if (1) their investments are kept for a minimum of 5 years, (2) earnings are reinvested during that period, and (3) they do not own directly, or indirectly, more than 25 percent of the companies capitalized (3).

Loans for Commercialization and Industrialization of Innovation are for activities in the start-up of a new commercial activity. In 1984, there were 238 loans for a total of FFr 220 million ($24.5 million). The interest charged is 3.5-4 percent per annum (3).

Credits for Long-Term Improvement are designed for innovation over a long period of time. The fund totals FFr 1 billion ($111.3 million) and the interest charged is 9.25 percent. The use of such a credit is obligatory for projects involving more than FFr 2 million ($222,500) (3).

EFFECTS OF THE CHANGE IN GOVERNMENT

The main impetus behind the Mobilization Program had been the Socialist government elected in 1981. The election of a conservative majority in the National Assembly in March 1986, has already led to some major policy changes. The Ministry of Research and Technology has been dissolved and a Minister Delegate for Research and Higher Education, Mr. A. Devaquet, appointed within the Ministry of Education. He will continue to have responsibility for CNRS and INSERM and possibly for research activities of other agencies. Though under strong pressure to reorganize CNRS and INSERM, he has promised to preserve their present structure for the time being.

However, the civilian R&D budget has been cut by 8 percent, with CNRS and INSERM losing $143 million and $39.5 million respectively. Ordinarily, the CNRS would have had the autonomy to implement the cuts according to its own priorities (i.e., minimizing its effect on operating budgets), but apparently this has not been acceptable to the Ministry of Finance. Though no decision has been announced yet, it is believed that the budget for the Mobilization Program in Biotechnology will be reduced by 20 percent.

These rapid measures by the new Chirac government have been met with disquiet by the scientific community, which is concerned about the loss of research funding and the reversal of the new policies that were being put in place by the Mobilization Program.

III. UNIVERSITIES AND RESEARCH INSTITUTES

Basic research in France is primarily carried out in the institutes of the government research organizations, many of which are located at the universities. Institutions of higher education are divided into universities and Grand Ecoles. The universities carry the primary responsibility for undergraduate and graduate education in the biological sciences, while the Grand Ecoles provide a rather unique combination of engineering and management. The most prominent universities in terms of biotechnology

research and training are: Paris, Toulouse, Strasbourg, Compiegne, and Montpellier. Five institutions have been designated as transfer centers responsible for bridging the gap between basic research and industrial applications. These are:

- o University of Compiegne: engineering techniques,
- o Pasteur Institute: genetic engineering,
- o National Institute of Agronomy, Paris-Grignon: molecular biology and process technology,
- o University of Aix-Marseille: immunology, and
- o University and National Institute of Applied Sciences of Toulouse: microbiology.

The research institutes visited were the Institute Jacques Monod and the Pasteur Institute in Paris, the institutes composing the Microbiology Scientific Group (GS million) in Toulouse and the Enzyme Technology Laboratory of the Technical University of Compiegne (UTC).

National Center of Scientific Research (CNRS) is the largest public research agency in France, with an annual budget (for 1984) of FFr 7.7 billion ($856.9 million) and a staff of 9,878 researchers and 15,082 technical and administrative staff (3). It is composed of seven departments, one of which is Life Sciences with 19.4 percent of the total budget. The budget and staff involved in biotechnology activities appears in Table 3, showing that it is the single most important research agency in this sector. The CNRS operates its own laboratories and units, as well as mixed units which have personnel from other organizations (e.g. university-CNRS institutes). In addition, there are units that are associated with the CNRS, organizations that collaborate with it on specific projects and CNRS scientific groups that provide technical support for research. In 1982, a new office was created within the CNRS, the Directorate for Commercialization and Application of Research (DVAR), which is charged with identifying those projects that may be of commercial value. The mechanism for detecting these projects is either through the action of CNRS researchers or by a request from industry for specific types of research. The DVAR collaborates on this effort with ANVAR (see below) leading to patenting of new products/processes and funding of mission-directed research through contracts (at the present time there are some 50 contracts with a total value of FFr 4 million ($445,000) and involving some 60 researchers) (3).

CNRS maintains some excellent laboratories, and its research priorities are listed in Table 3. In addition, it has been asked to increase its efforts in basic and applied enzymology, expand opportunities for young researchers, and participate in development of new laboratory equipment. During the past few years, the CNRS has come under severe criticism for its research policies and for its lack of interaction with other institutions, both public and private. At the research level, it must be noted that all CNRS staff are civil servants, and as such, their positions are protected. This has made the

organization very inflexible and sluggish in pursuing new research directions. It is this structural problem that is blamed for some of the large gaps in the French research effort (e.g. plant molecular biology, protein engineering, downstream processing). In order to create a new group, the principal investigator is appointed and then negotiates for the necessary resources. In other countries, it is common for the principal investigator to negotiate for his group prior to his appointment. This frequently results in the creation of new groups that are both undercapitalized and undermanned. The poor record in technology transfer is also blamed on the relative isolation of the research groups, the most glaring example of it being the slow dissemination of the new technologies to other public and industrial laboratories.

National Institute of Health and Medical Research (INSERM) is the principal agency in biomedical research and applications with a total budget for 1985 of FFr 1.5 billion ($166.9 million) and a staff of 1,855 researchers and 2,466 technical and administrative support (3). A summary of its budget and personnel involved in biotechnology appears in Table 3. INSERM maintains its own research units, funds individuals working in other organizations and has contracts to outside organizations. The basic research priorities for INSERM are also outlined in Table 3. In addition, INSERM bears responsibility for application of the new technologies to the major diseases such as cancer and cardiovascular disorders, including new diagnostic kits and therapies.

INSERM is considered to have performed adequately both in basic and clinical research, though as in the case of the CNRS, it is felt that the new technologies have been slow in filtering down to the clinical laboratories. While the three major French pharmaceutical groups are among the largest investors in R&D (total annual R&D: FFr 450 million ($50.08 million)) (3), the coordination with public research has been inadequate.

National Institute of Agronomic Research (INRA) is the principal research agency in the agro-food sector, and extremely important from the political and economic viewpoints. Revenues in the food industry were FFr 472 billion ($52.5 billion) and in agriculture, FFr 322 billion ($35.8 billion). The total profits were FFr 25.8 billion ($2.87 billion) for 1984 (3). Traditionally, INRA has lagged behind in basic research, while the industrial sector is fragmented and has a poor record in R&D. Though INRA has a large budget [FFr 2.1 billion ($233.7 million)], only a small fraction is spent in biotechnology, though (as noted in Table 3) most of its scientists are supposed to be involved in biotechnology related activities (3). The basic research activities of INRA are also outlined there.

Many of the weaknesses in French biotechnology fall under the responsibility of INRA (plant molecular biology, enzymology, plant and animal breeding, fermentation technology, bioconversion). A major effort is being made to restructure INRA, taking advantage of the fact that its director has a greater autonomy than his counterpart at the CNRS. Budget constraints make it impossible to launch many new initiatives, so particular attention has been paid to international cooperation within the framework of the European Community. This is of particular importance in plant biology, artificial

seeds, and bioengineering (with average grants of ECU 120,000 ($195,012)* for periods of 3-4 years).

The PASTEUR INSTITUTE is considered to be the "jewel in the crown" of the French biological sciences. It is a private foundation, to which the government contributes 50 percent of its budget (FFr 243.5 million ($27 million) for 1985). Table 3 shows the budget and staff involved in biotechnology activities. The remainder of the financial support comes from internal resources (25.5 percent), industrial contracts and royalties (13.5 percent), and private financial support (11 percent) (6).

Traditionally, the Pasteur Institute has been involved in fundamental research in biology as well as in biomedical areas (the project areas appear in Table 3). An expansion of its activities is envisioned in: yeast molecular biology, fermentation technology in the food industry, development of biological pesticides, and cooperative research with less developed countries in infectious diseases. The Institute will also become a major resource for computer data banks on nucleic acid sequences, bacterial strains collections, service of DNA and peptide synthesis, and training services.

In order to maximize the impact of the Institute on the industrial sector, it has formed four separate companies or joint ventures (7). These are :

- o PASTEUR VACCINES: production of vaccines and sera. It is owned 49 percent by the Institute and 51 percent by the Institut Merieux.
- o DIAGNOSTICS PASTEUR: diagnostics (early product will be the AIDS kit). It is 49 percent owned by the Institute and 51 percent by Sanofi.
- o BIOCHEM: development of biological pesticides. Institute involvement is 15 percent and 85 percent from Solvay.
- o GIRPI: research on the production of immunostimulants. Three equal partners: Institute, CHOAY and Sanofi.

The two largest companies, Pasteur Vaccines and Diagnostics Pasteur, were already well developed activities. Approximately 50 percent of vaccine production is now sold abroad, and diagnostics production is also oriented in that direction (particularly with the introduction of the AIDS kit).

Following the patenting of any new discovery at the Institute, the affiliate companies spend some six weeks examining it, and then have three months in which to decide whether to commercialize it. A significant number of American companies have working arrangements with them. Mentioned were Beckman in the area of instrumentation, and Abbott in diagnostics.

It was stated that the Institute possesses a greater degree of flexibility than the other government research organizations since, of its total staff of

*Average exchange rate for 1985: European currency unit (ECU) = $1.6251.

2,000, only some 450 are permanent members of the scientific staff (some 500 French and foreign scientists are on short-term appointments for training purposes) (6). In addition, since their funding is not totally government, they can obtain grants and contracts from the private sector in order to establish new groups. This is the mechanism used to create the new group of Julian Davies which will do research into the biology of streptomyces and antibiotic production.

(a) Financial support: Most of the funding for the research institutes visited comes from the CNRS and to a lesser degree from INRA and INSA. The total support from these agencies is in the order of $78 million (Table 3) plus an additional $10 million from the Mobilization Program (1). This represents a real expansion in the resources available, with an important part being used for the remodeling of laboratories and the upgrading of laboratory equipment. As would be expected, the institutes whose research objectives are in line with those of the Mobilization Program are the ones that seem to have benefited the most (e.g., Toulouse, Compiegne). There is serious concern now as to the effects of the budget cuts announced by the new government. Since salaries and fixed costs account for more than 75 percent of the budgets, this could lead to reductions of up to one-third in operating funds.

(b) Scientific Research: The quality of basic research shows an uneveness that is somewhat surprising given France's history and its traditional strengths in modern biology. Tables 4 and 5 give an overview of the principal research themes at several major institutes and laboratories. Work of international quality was found in many topics (e.g., DNA repair, bacterial cell cycle, retroviruses, symbiotic nitrogen fixation). The scientific environment differed markedly not only between Paris and the centers in Toulouse and Compiegne, but also between the two centers in Paris.

The Institute Jacques Monod is a joint University of Paris-CNRS institute. A visit to the institute provided some insight into the workings of the university, the CNRS and the new Mobilization Program. Following his appointment, each new CNRS leader has to negotiate for the resources necessary to run his group. This can be done in one of two ways: obtaining a permanent budget covering most of his costs or having a minimum budget and applying for grants. While the first choice gives a great measure of stability, the large commitment and expense in staff positions makes for a lack of flexibility, should he later choose to change the direction of his research. In the second case, he gains flexibility, but is forced to apply constantly for grants which are relatively small (e.g., FFr 80,000 ($8,900) from CNRS; $25,000 from EEC) (9). In most countries, it is felt that postdoctoral fellows are a key element in research. However, the French system does not allow for such temporary appointments.

The Pasteur Institute is an historical institution that houses a number of the best French groups. French research has frequently been described as "cloistered" and "vertical." Productive research in biotechnology is likely to be horizontal, in that it involves collaboration between groups with different areas of expertise. In a "vertical" arrangement, communication and collaboration flows among groups in the same research area. Even then, this is most likely to occur between those individuals with an historical

Table 4.
RESEARCH INSTITUTES VISITED

	Institute Jacques Monod	Pasteur Institute	Laboratory of Enzymatic Technology
Affiliation	CNRS[1]-University of Paris		CNRS-INSERM[2]
Primary Research Interests	Structure & function of DNA Biochemistry of chromatin Protein structure Gene expression of vaccinia virus Plant viruses (TYMV) Molecular immunology Cell biology of membranes DNA mismatch repair DNA replication & cell cycle Protein secretion Developmental biology in drosophila Biochemistry of development	Molecular genetics of bacteria & their viruses Gene expression during embryogenesis Molecular biology of nerve synapses Mechanisms of immune response Pathogenesis of infectious diseases Vaccine development Animal virology	Enzyme kenetics Modulation & stabilization of enzymes Cell immobilization Enzymatic electrocatalysis Enzymatic reactions in non-aqueous conditions Enzymatic therapy Extraction & purification methods

1 Centre National de la Recherche Scientifique (National Center of Scientific Research)
2 Institut National de la Sante et de la Recherche Medicale (National Institute of Health and Medical Research)

Table 5.
MICROBIOLOGY SCIENCE GROUP OF TOULOUSE

Laboratory	CNRS Research Center in Biochemistry and Cellular Genetics	CNRS/INRA Laboratory of Plant-Microorganisms Interactions	Department of Biochemical Engineering, University Paul-Sabatier	CNRS Laboratory of Control System Analysis
Principal Research Themes	Bacterial transformation & recombination Bacterial cell cycle Transposition in bacteria Genetics of antibiotic production Genetics & molecular biology of retro-viruses Synthesis & assembly of ribosomes in animal cells	Mechanism of symbiotic nitrogen fixation Genetics of plant pathogen, pseudomonas solanacearum Structure & gene expression of plant viruses	Plant cell culture in suspension Enzymatic synthesis of fine chemicals (group transfer, cofactors, non-aqueous media) Microbial physiology during industrial production	Fermentation processes Modeling Control algorithms Instrument development Computer control

CNRS=Centre National de la Recherche Scientifique (National Center of Scientific Research)
INRA=Institut National de la Sante et de la Recherche Medicale (National Institute of Health and Medical Research)

relationship (e.g., mentor to previous student). Apparently, these problems are not unusual in the laboratories in the Paris area, including the Pasteur and the Institute Jacques Monod. The GSM in Toulouse is composed of four separate laboratories and is probably second in size only to the group of laboratories in the Paris region. However, the GSM seems to have a much more cohesive and interdisciplinary character to it, with active collaboration between the different laboratories. The same is true of Compiegne, which appears to have the most comprehensive biochemical engineering program in the country, though some of the more biological research is carried out in collaboration with laboratories elsewhere.

(c) University-Industry Interactions: The poor record of French industrial R&D makes research institute-industry interactions one of the priorities of government policy. The mechanisms used are: consultantships, assignment of company researchers to academic laboratories, industrial contracts, and joint ventures. The Pasteur Institute has been the most active in all respects, particularly having a large contract from Rhone-Poulenc and several corporate joint ventures. These are an outgrowth of its long established activities in public health. The UTC has research contracts with 20 companies, 14 of which are French. The total income from these contracts ranges from FFr 10-12 million ($1.11-$1.34 million) annually (10). Also, the engineering students are required to spend a training period in industry, often at company expense. The GSM at Toulouse has a technology transfer center for the application of its research findings in the sectors of biochemical engineering and food processing. They receive industrial contracts, have five to six researchers on secondment from industry, and enjoy a good relationship with the Sanofi research center at Labege. The GSM has also spun off a new firm, BioEurope. On the other hand, the Institute Jacques Monod has very little involvement with the Mobilization Program or with private industry.

The Mobilization Program has promoted industrial relationships with both the GSM and the UTC, though given the characteristics of these organizations under the leadership of Professors Durand and Thomas respectively, it is likely that this would have happened in any case. The greater challenge is whether the situation will improve at institutes such as the Jacques Monod, which is more representative. The industry officials interviewed showed some interest in these kinds of arrangements, but were skeptical as to whether they would meet company needs.

(d) Staffing: The government freely admits that there are severe problems in the areas of microbiology, plant biology, and biochemical engineering. In addition, the distribution of specialists to different geographical centers is judged to be inadequate. As mentioned earlier, since most research appointments are in the civil service, the creation of a new research group is not a trivial matter.

(e) Education: An historical element creeps in with the dual system of the universities and the Grand Ecoles. The students of the Grand Ecoles go through a stringent selection process based on logic and mathematics. Research is not an important aspect of their education (usually only 5 to 10 of each class of 350 does a research project). In each class, the top 50 go into administrative positions in government or in state industries, but seldom into science or engineering.

The university system, faced with the demands of mass education, has little selectivity in its admission policy and limited resources for research. The undergraduate program consists of three cycles. The first consists of 2 years of general studies. The second consists of two 1-year programs, the first leading to a "license" and the second to a "maitrise." An additional year of advanced courses (and/or research) leads to the Diploma of Advanced Studies. Under a new reform law, this would be followed by a 3-year program for a Ph.D. The current Ph.D. programs are uneven, with the best students doing their theses in public research institutes with qualified researchers and modern equipment. The new government has declared its intentions to change the Ph.D. program once more. The previous Socialist government had introduced the FIRTECH program which required engineering students to do a research project during their training.

Critics of the dual Grands Ecoles/universities system have pointed out that this educational system has a double negative effect: it skims off the best candidates for a science/engineering career, and then channels them away from research and technology. At the same time, it is this elite that will make policy without having had the appropriate practical experience.

IV. INDUSTRY

The French companies that have exploited the new biotechnologies are limited in number (see Table 2). The principal activities revolve around three major industrial groups: Rhone-Poulenc, Sanofi and Roussel-Uclaf. In the past few years, there has been the appearance of a series of new venture capital-funded companies (Table 6). It is worth noting that the level of capitalization (with the exception of Transgene) is minute, suggesting that they can only operate on the basis of contract R&D to larger organizations (public or private).

SANOFI is the health care group of the huge Elf-Aquitaine oil conglomerate (which owns 60 percent of it). The facts about Sanofi appear in Table 7. Increases in sales have primarily occurred abroad, with 50.5 percent of sales outside of France (most rapid growth has been in perfumes and beauty products). Investments in R&D in 1984 were primarily in the pharmaceutical sector: FFr 803 million ($89.4 million). Investment in plant and equipment modernization that same year totalled FFr 467 million ($51.9 million) (11).

At the end of 1984, Elf-Aquitaine restructured all of its biotechnology related activities around Sanofi. It created Elf Bio-Industries, which is 65 percent owned by Sanofi and 35 percent by Elf-Aquitaine. This new company is expected to have annual sales of FFr 4 billion ($445 million) in 1985, with business in the following sectors (11): gelatins, fats, and proteins; fragrances, flavors, and food additives; and seeds, animal health, and nutrition. The primary effect of this reorganization is that the Sanofi group will now have total sales of FFr 14-15 billion ($1.56-$1.67 billion) and the proportion of agro-food activities will increase from 10 percent to 28 percent (11). However, the single largest business would still be pharmaceuticals. The first application of the new technologies by Sanofi was the production of human growth hormone and growth release factor.

Table 6.
NEW BIOTECHNOLOGY COMPANIES
AND THEIR AREA(S) OF INTEREST

	Date Created	Amount Capitalized (in millions of $)	Research Area(s)
Transgene	1981	11.0	Genetic engineering
Immunotech	1982	2.0	Diagnostic kits
Clonatech	1984	2.0	Diagnostic kits
Valorga	1981	0.73	Continuous waste biodigestion
Biosys	1981	0.35	Bioluminescent elisa analytical kits
France Embryon	1980	0.14	Embryo transfer techniques
CIRTA	1980	0.1	Contract research: chemistry & biochemistry
Germe	1979	0.06	Microbiology
Transia	1984	3.0	Agro-food
BioEurope	1985	1.2	Food & fine chemistry

SOURCE:Monsan, Pierre F., "The Industrialization of Biotechnology in France. Recent Developments.", Abstract prepared for The 1st International Conference of Biotechnology, Osaka, Japan, November 5-8, 1985.

BEST COPY AVAILABLE

Table 7.
CHARACTERISTICS OF COMPANIES VISITED

	Sanofi	Rhone-Poulenc	Roussel-Uclaf	Transgene
1985 Annual Sales in FFr($)*	14.5bn($1.61bn)	56.1bn($6.24bn)	11.81($1.31bn)	30M($3.34M)
1985 Net Profit in FFr($)*	480M($53.42M)	2.31bn($257M)	519M($57.76M)	None
Government Participation	60% owned by state controlled Elf-Aquitaine group	100% state owned	40% state owned	36% owned by three state controlled corporations & 15% by government organizations
Business Sectors	Human Health 47% Perfumes & Beauty Products 27% Bio Industries 26%	Chemicals 39% Health Products 22% Agrochemicals 11% Textiles 22% Films & Systems 4% Other 2%	Pharmaceuticals 51% Agroveterinary 25% Industrial Chemicals & Biological Products 12% Consumer Products 10% Other 2%	Contract R&D for the development of bacterial strains & mammalian cell lines for industrial production.
R&D Expenditures in FFr($)*	1.04bn($115.7M)	2.7bn($300.5M)	1.159bn($128.98M)	N/A
Areas of R&D	Anticonvulsants, hypnotics & anti-depressants Cardioprotective agents Anti-arthritic agents Anti-tumor agents Prevention of growth disorders Nutrient dense animal feeds Genetic modification of crop plants Food additives: polysaccharides & sweeteners Plant biology	Antibiotics Cardiovasculars Anti-infectious agents Anti-depressants & tranquilizers Anti-rheumatic agents Gastrointestinal drugs Anti-cancer drugs Immunomodulators Animal vaccines & sera Animal feed additives Biopolymers	Antibiotics Vitamin B-12 & derivatives Anti-inflammatory steroids Genetic Engineering Lymphokines Immunology	Cloning & expression of alpha-interferon, IL-2, & Factors VIII & IX Cloning & expression of alpha-1-anti-trypsin & analogs Product against poison ivy antigens Anti-coagulant production New lactic bacteria strains New brewer's & baker's yeast strains

*Average exchange rate for 1985:FFr8.9852=$1.
M = millions, bn = billions

BEST COPY AVAILABLE

RHONE-POULENC is the large and highly profitable nationalized chemical group (Table 7). Chemicals represent its largest business sector, and is divided into three operational divisions. Of these, the Health Division is the largest with four separate programs: human health care, veterinary health care, animal related products (e.g., feed) and bulk chemicals (intermediates for drug production). Though exports accounted for 50 percent of sales, Rhone-Poulenc's market share in the key U.S. and Japanese markets remained weak. Rhone-Poulenc also owns 51 percent of the Institute Merieux, a well established producer of vaccines and blood products (12).

Just as other chemical multinationals, Rhone-Poulenc is moving into new high-value added products, particularly pharmaceuticals. This strategy consists of four aspects:

(1) Construction of a new biological research center at Vitry: this will concentrate on molecular biology and cell biology and will have a staff of 1,200 (12).

(2) Agreements with government research organizations: it pioneered in establishing contracts with CNRS, INSERM and INRA.

(3) Investment in computerized drug design: Rhone-Poulenc spent FFr 51 million ($5.68 million) in 1985 for new software. New data systems will account for 2.5 percent of its 1986 R&D budget (13).

(4) Acquisitions: Rhone-Poulenc is planning to raise FFr 1 billion ($111.3 million) for expansion and development (14). It has acquired a U.S. biotechnology company, Purification Engineering, and established a new subsidiary, IBF Biotechnics (synthetic serum, separation chromatography matrixes). The Institute Merieux has acquired a 51 percent stake in the U.S. company Virogenetics (vaccines) (15). It also had a research contract with Calgene for the development of a herbicide resistant sunflower plant. In France, it has bought 10 percent of the sugar beet producer Ceres, as well as the corn seed development program of the National Union of Cereal Agricultural Cooperatives (16).

An internal study had shown that the costs of drug development were highest in the U.S., followed by France and the U.K. The productivity, however, was approximately the same for the U.S. and the U.K., but considerably lower in France. It is likely that expansion through acquisitions and R&D activities outside of France will continue.

Rhone-Poulenc is among the state-owned groups that the Chirac government has earmarked for privatization. It is unclear when this is likely to take place and what effect such a move will have on corporate business strategy.

ROUSSEL-UCLAF is the French pharmaceutial group which is 54.5 percent owned by the German Hoechst chemical group and 40 percent by the French government (Table 7). Its export sales represent 71 percent of total sales, with North America accounting for 10 percent and Asia/Oceania 17 percent of total sales (17). The principal interest of the Hoechst group has been Roussel-Uclaf's drug research leading to new products and it has encouraged biotechnology activities.

In addition to its own in-house research, Roussel-Uclaf has signed general cooperation agreements with CNRS, INRA, INSERM, and CIRAD (Agency for International Cooperation in Agronomical Research for Development) leading to a number of research contracts in government laboratories. Along with Sucre Union (a major French sugar producer) it has created BioEurope, a contract R&D company located in Toulouse (Table 6). Two major research areas for BioEurope are the application of molecular biology for plant protection and improved yields, and the use of enzymes in food processing.

In conjunction with American Hoechst, it has established a new company in the U.S., Roussel Agri-Vet Company, for the production and marketing of agrochemicals and veterinary drugs. It has sold Foster Grant, its U.S. sunglasses maker, but intends to maintain the funds in the U.S. so as to reinvest them in sectors that are compatible with its primary business interests.

TRANSGENE is the leading new biotechnology firm in France. It was started in 1980 by two scientists, Professor Pierre Chambon of the University Louis Pasteur in Strasbourg, and Dr. Philippe Kourilsky of the Pasteur Institute. The company had a capitalization of FFr 81 million ($9 million) for 5 years (5). Two-thirds of the shares are held by: Paribas (an investment bank), Assurances Generales de France (AGF, an insurance group), BSN (food products), Elf-Aquitaine, and Moet Hennessy (wines). Another 23 percent is held by non-profit organizations: University of Strasbourg, INRA, INSERM, CNRS, Pasteur Institute, and the Foundation for Research in Molecular Genetics. (This foundation was created by Chambon in order to fund basic research.) The remainder is held by individual shareholders, primarily Transgene staff (18).

The laboratory in Strasbourg has a staff of 100, of whom 40 are scientists and 40 are technicians. They also have close ties with Chambon's laboratory which has some 126 Ph.D's. Transgene is a contract R&D firm that develops bacterial strains and mammalian cell lines for industrial production. It operates on the basis of contracts, licenses and joint ventures. Some 60 percent of their contracts are in the area of health care (Table 7).

The company is formed of a number of groups: DNA synthesis, genetic engineering, biology of yeast and B. subtilis, mammalian biosystems, fermentation, and proteins.

Annual turnover is around FFr 30 million ($3.34 million) (19), not sufficient to be profitable, but they hope to reach the breakeven point in one or 2 years. Transgene has these characteristics: it is strictly a contract R&D operation, funded by French companies and institutions, and targeted primarily at French industries (though they would claim that their market is all of Europe). Even in this new biotechnology "start-up," the government plays an ubiquitous role. Three of the corporate shareholders (Paribas, AGF and Elf-Aquitaine) are government-controlled and hold 36 percent of the shares (18). Another 15 percent is held by government organizations, making a total of 51 percent. Of the companies whose contracts have been disclosed (Roussel-Uclaf, Institut Merieux, Centre National de Transfusion Sanguine, Sanofi, and Pasteur Institute), most are also government-controlled. Though the corporate statement is that Transgene is, and operates as, a private company with private clients, it cannot but be affected by government policy.

INDUSTRIAL OVERVIEW

The central role of government in industry makes France unique. The government policy of "filieres" defines new technology sectors and involves the state at each step of industrial innovation starting with basic research. R&D is heavily concentrated in large companies -- of 1,500 companies with R&D activities, 100 companies with more than 50 researchers each did 75 percent of the industrial R&D and received 90 percent of the public support. In 1982, the nationalized firms received FFr 8.4 billion ($934.8 million) out of the total of FFr 10.5 billion ($1.17 billion) in government support, or 80 percent. The chemical and pharmaceutical industries received 9 percent and 6 percent respectively (5). Not only do large companies conduct most of the R&D (as happens elsewhere), but they are also likely to be nationalized as well as supported by the government. In spite of this, French industry compares poorly in the number of personnel involved in R&D [the U.S. has 14 times more than France, Japan 5.5 times, Germany and the U.K. 2.5 times (20)]. In addition, the proportion of industrial R&D in the private sector is lower than in other industrial nations [43 percent in France versus 50 percent in the U.S., 58 percent in Germany and 64 percent in Japan (20)]. State ownership of major companies is likely to decrease under the privatization policy of the new government. It has already announced that Rhone-Poulenc will be sold off to the private sector.

Industrial development in biotechnology is closely allied to the fortunes of three industrial groups: Sanofi, Rhone-Poulenc and Roussel-Uclaf. The major business sector is pharmaceuticals, with agro-food becoming increasingly important. There are a number of small new biotechnology companies, but they are unlikely to have a major impact in the short-term. The government has full or partial ownership of the three major groups, this also being true of Transgene. In terms of their markets, France still represents a very important segment of their total sales [29 percent for Roussel-Uclaf (17), 41 percent for Rhone-Poulenc (12), and 50 percent for Sanofi (11)], while their penetration of the all-important U.S. and Japanese markets is still weak. All three are committed to expanding their efforts in biotechnology and to establishing themselves firmly in foreign markets. In order to do so, they have expanded their research efforts in biotechnology, and entered into agreements and contracts with government research agencies. In general, the industrial view is that these contracts and the efforts of the Mobilization Program have had a limited impact on technology transfer from public research laboratories. They are also convinced that the most important work will be carried out in-house. All three groups have made it known that they intend to acquire technology and companies abroad (preferably in the U.S.). As indicated, a number of these acquisitions have surfaced, but they are still relatively few in comparison to those of other European multinationals.

V. CONCLUSION

At the beginning of this decade, France realized the importance of the new biological technologies, and that industry lacked the resources to compete effectively. The ambitious Mobilization Program for the Development of Biotechnologies was drafted to meet this challenge. This Program was never

fully implemented due to a change in the French economy, and the Draft Law for 1986 reflects a much more modest effort in spite of the rhetoric. The reduction of research budgets, as well as the reorganization of research agencies under the new government, will inevitably impede further implementation of the Program.

The involvement of the government in biotechnology is ubiquitous. The state frequently acts as researcher, administrator, producer, client, and banker. This policy has been successful both technically and financially in the case of massive, government projects such as Mirage jet fighters and nuclear reactors. Its performance has been less impressive when approaching multiple, private customers as in the computer industry. Therefore, it is useful to examine how the government in general, and the Mobilization Program in particular, affects the different elements of biotechnology.

Research: The emphasis that the government has put on biotechnology has had a generally beneficial effect, both politically and in generating public support. In the public institutions, basic research in biology had been allowed to languish during the 1970's. (During the period from 1967 to 1979, government support of R&D decreased from 2.15 percent to 1.82 percent of the national budget.) A clear indication of that is the present effort to refurbish facilities, re-equip laboratories in order to carry out the new technologies, and establish laboratories in new project areas. This would not have been required if the research establishment was at an internationally competitive level. Neither in absolute, nor in relative terms, are the budgets particularly large (e.g., let us compare them with figures for the Netherlands):

	France (5)	Netherlands (21)
Public R&D	$78.00 million	$31.2 million
Special biotech programs	$13.75 million	4.4 million
TOTAL	$91.75 million	$35.6 million

Therefore, France barely spends 2.5 times more than the Netherlands for research in this domain, while its GDP is 3.6 times larger. Perhaps more important is the fact that France (with limited resources) intends to become a major competitor in biotechnology, with a presence in all industrial sectors. This is in sharp contrast to the Dutch policy of concentrating on specific industrial niches.

The structure of the French research establishment presents serious difficulties due to its inflexibility, civil service mentality and fragmentation into small units with limited resources. There is a marked difference between Paris and the regional centers of Toulouse and Compiegne. The latter appear more innovative, with greater collaboration between institutes and better contacts with industry. It was generally felt that being located outside Paris provided more scope for new initiatives, with regional support, though small, allowing more flexibility. Even a vast infusion of new funds (an unlikely possibility) would have a limited effect in

the absence of a better integration of research efforts in government agencies and universities. The creation of numerous agencies, commissions, directorates, and offices with conflicting and overlapping areas of responsibility, creates a maze that is difficult for an outsider to understand and for an insider to use.

In industry, the situation is equally serious. The three major corporate groups are tooling up and have expanded their R&D efforts, but this is again an effort to play catch-up with the competition. The creation of a new biotechnology center at Labege, the construction of a center at Vitry, and heavy investment in new equipment, clearly reflect industry's efforts in that respect.

Industrial Development: France has started out in a vulnerable position. The number of companies with biotechnology activities and expertise is small, and their primary concern has to be a defense of their own domestic market already subject to foreign penetration. They also have to develop new products and processes and direct these towards world markets. The presence of the three major groups in the two key markets of the U.S. and Japan is very limited, while Transgene's business strategy seems to be directed only to France in the short-term. Though Transgene may be competitive commercially, all of the products or processes identified were being carried out at an equal or more rapid rate elsewhere.

The official view is that the French educational system provides an adequate pool of scientists (with the exception of microbiologists, plant molecular biologists and biochemical engineers). However, it was mentioned that 50 percent of the scientific staff at Transgene was foreign, and a large proportion of the genetic engineering specialists at Labege were also of foreign extraction. In both cases, this foreign staff came from other European countries. None of the industrial managers felt that the Mobilization Program had a direct impact on their business. However, it had improved the funding for basic research and altered the attitudes of academic researchers towards industrial projects.

Finally, one senses that French biotechnology suffers from a state of not-so-splendid isolation. There are several indicators of this: (1) in visits to 11 European countries, France was the only one where a significant proportion of senior government officials and corporate managers had a limited knowledge of English; (2) the small number of French researchers in other European countries, the U.S. or Japan; and (3) the scarcity of French technical managers with extensive experience abroad (possibly a reflection on the French educational system). At the same time, there are signs of change. France is trying to make its research and educational programs more compatible with those of its major partners by encouraging French researchers to spend periods abroad, promoting projects within the framework of the Eureka and EEC programs, and trying to establish new biotechnology companies. In this respect, there is considerable interest in establishing closer ties with U.S. biotechnology companies and in trying to attract some of them to France.

Finally, the eventual success or failure of French biotechnology is most likely to depend on whether the government will continue its long "dirigiste" tradition (which has been independent of the particular administration in power) or will shift to a more flexible, market-oriented approach to industrial innovation.

ACKNOWLEDGEMENTS

Chantal Masquelier, Delegue Commercial, American Embassy, Paris

Babette Orr, Commercial Officer, Foreign Commercial Service, American Embassy, Paris

Willian Tagte, Commercial Attache, Foreign Commercial Service, American Embassy, Paris

Patti Litman, Science Attache, American Embassy, Paris

Manfred Czielsla, European Representative, National Science Foundation, American Embassy, Paris

REFERENCES

1. Lederman, Leonard L., "Recent Changes in Science and Technology Policy, Priorities, Practices, and Programs in France, Federal Republic of Germany, the Netherlands, Sweden, and United Kingdom," National Science Foundation, Washington, D.C., December 1984.

2. Ministere de la Recherche et de l'Industrie, Programme mobilisateur: l'essor des Biotechnologies, 1982.

3. Projet de loi de Finances Pour 1986.

4. U.S. Department of Commerce, International Trade Administration, "High Technology Industries: Profiles and Outlooks, Biotechnology," Washington, D.C., July 1984.

5. Monsan, Pierre F., "The Industrialization of Biotechnology in France: Recent Developments," Abstract prepared for The 1st International Conference of Biotechnology, Osaka, Japan, November 5-8, 1985.

6. Department of Applications of Research in Collaboration with the Heads of Departments of the Pasteur Institute, 1985.

7. van Robais, Xavier, Institut Pasteur, Paris, France, personal communication, December 1985.

8. Financial Times, London, June 10, 1986.

9. Radman, Professor Miroslav, Institut Jacques Monod, Paris, France, personal communication, December 1985.

10. Thomas, Daniel, and J.N. Barbotin, Laboratory of Enzymatic Technology, University of Technology of Compiegne, France, personal communication, June 13, 1986.

11. Sanofi Annual Report, 1984.

12. Bost, Pierre, Director of Research, Rhone-Poulenc, personal communication, June 10, 1986.

13. Scrip, March 17, 1986.

14. Financial Times, London, September 11, 1985.

15. Chemical Week, March 19, 1986.

16. Chemical Week, November 20, 1985.

17. Roussel-Uclaf Annual Report, 1985.

18. Garry, A.B., Transgene: A Presentation, November 1985.

19. Eisenmann, Etienne, Director, Transgene, Paris, France, personal communication, December 12, 1985.

20. Salomon, Jean Jacques, "Le Gaulois, Le Cowboy et le Samourai," Rapport sur la politique francaise de la technologie, Centre de prospective et d'evaluation, Paris, France, July 1985.

21. Schilperoort, R.A. & van der Meer, R.F., "National Biotechnology Development Programmes and Strategies (The Innovation-Oriented Programme on Biotechnology in the Netherlands)," January 1985.

APPENDIX

ORGANIZATIONS AND INDIVIDUALS VISITED

Government

Mobilization Program in Biotechnology: Dr. Gilbert Durand, Director until September 1985. Dr. Daniel Thomas, present Director.

CNRS (National Center for Scientific Research): Mrs. France Normand, Coordinator for Technology Transfer.

INRA (National Institute for Agronomic Research): Dr. Andre Berkaloff, Scientific Adviser to INRA.

Research Institutes

Institut Pasteur: Mr. Xavier van Robais, Head of the Service of Research Commercialization. Dr. Antoine Danchin, Group Leader. Dr. Julian Davies, Head, Microbiology Section.

Institut Jacques Monod, University of Paris VII: Dr. Francois Chapeville, Director. Dr. Miroslav Radman, Group Leader.

CNRS Center for Research in Biochemistry and Cell Genetics, Toulouse: Professor J.P. Zalta, Director.

INRA Laboratory of Molecular Biology--Plant-Microorganism Interactions: Dr. J. Denarie, Research Director.

Department of Biochemical Engineering, University Paul Sabatier, Toulouse: Professor Gerard Durand, Director. Professor G. Goma, Director of Transfer Center.

Laboratory of Enzymatice Technology, Technical University of Compiegne: Professor Daniel Thomas, Director. Dr. J.N. Barbotin, Staff Scientist.

Industry

SANOFI: Mr. Paul Prunet, Director of Development for Biotechnology Life Sciences Research Center, Labege: Dr. Paul-Henry Schmelck, Director.

Rhone-Poulenc: Dr. M. Raynaud, Director of Research.

Transgene: Mr. Etienne Eisenmann, General Director.

Genex International: Dr. A.C. Jouanneau, Vice President.

Other

Center of Research, Science, Technology and Society, National School of Arts and Crafts, Paris: Professor Jean-Jacques Salomon, Director.

Biofutur: Mr. Jeen Comar, Editor.

SEPFI: Mr. Bernard Leon, Director (organizes scientific conferences).

SECTION B

BIOTECHNOLOGY IN THE FEDERAL REPUBLIC OF GERMANY

SUMMARY

West Germany has the largest concentration of biotechnology activities in basic research and industrial activity. Government policy has given strong support to basic research in the universities and in the institutes of the Max Planck Society. Funding is provided by grants given through the German Research Foundation, or directly to the Max Planck Society. Technology transfer and commercialization of the new biotechnologies has been considered inadequate. The Federal Ministry of Research and Technology has promoted technology transfer by funding gene centers at four academic locations (Cologne, Heidelberg, Munich, and Berlin), establishment of two biotechnology centers, and support of joint university-industry projects through grants and contracts. Industrial innovation has traditionally been the province of the large chemical and pharmaceutical firms, which have extensive capabilities in research and development and production, as well as financial resources. Most German firms have been conservative in exploiting the potential of the new biotechnologies, but are now committing major resources to this area, though much of the R&D investment has been abroad. Though the government has tried to stimulate the creation of new entrepreneurial biotechnology firms, the number of such enterprises is still very small and their commercial viability very much in doubt. Germany is in a strong position, but still must meet the challenge of a more effective integration of its strong basic research establishment with its well developed industrial base.

I. INTRODUCTION

The Federal Republic of Germany has the strongest economy in Western Europe, and is one of the closest allies of the U.S. The German economy is into its fourth year of expansion, and 1986 is expected to show the best performance since 1979. The 1986 GNP growth is predicted to be 3-3.5 percent, with an inflation rate of less than 2 percent. There is serious concern about the imbalance in the economy as rapid expansion in exports and capital goods contrast with a sharp fall in the construction sector and a stagnation in consumer goods. Unemployment has remained persistently high at approximately 9.3 percent. There are also sharp discrepancies between the declining laender (states) of the north and the rapidly developing laender of the south. The northern laender's share of the total German GDP was 50.9 percent in 1960, but dropped to 48.5 percent in 1970 and 46.6 percent in 1983 (1).

The conservative government of Prime Minister Kohl was elected in late 1982 and has pursued policies of structural adjustment. Economic analysts have emphasized labor flexibility and the establishment of tax and labor policies that promote the creation of new, small and medium-sized companies, preferably in high technology sectors. The German federal government has followed such policies, while making major efforts at reducing the federal budget. Unlike the U.S., the German government, both at the federal and state levels, plays a key role in stimulating the transfer of new technologies from research institutions to industry. Biotechnology has been identified as one

of the key technologies of the future, and the federal government announced a national plan for biotechnology with a budget of $330 million for the period 1985-88.

The U.S. is West Germany's second largest export market, after France, while the U.S. ranks fifth among West Germany's suppliers. Principal U.S. sales to West Germany are in the areas of machinery, chemicals, electrical equipment, and aircraft. High technology products represent an important proportion of such exports, particularly in computers, electronic components, scientific equipment, and health care products and services.

II. GOVERNMENT POLICY

Federal policy affecting research and development (R&D) has undergone significant changes since the election of the Kohl government. Federal support for basic research has increased, while there is more emphasis on a market-oriented approach to industrial R&D and technological innovation. West Germany's total spending on R&D is approximately 2.6 percent of GDP, of which approximately 60 percent is spent by the industrial sector. This makes West Germany the leader in R&D investment in Western Europe (2). Figure 1 summarizes the government structure (both federal and state) of the R&D system in West Germany. The Science Council (Wissenschaftsrat) is the highest body responsible for the coordination of science policy and is composed of representatives from federal and laender ministries, universities, research institutes, and industry.

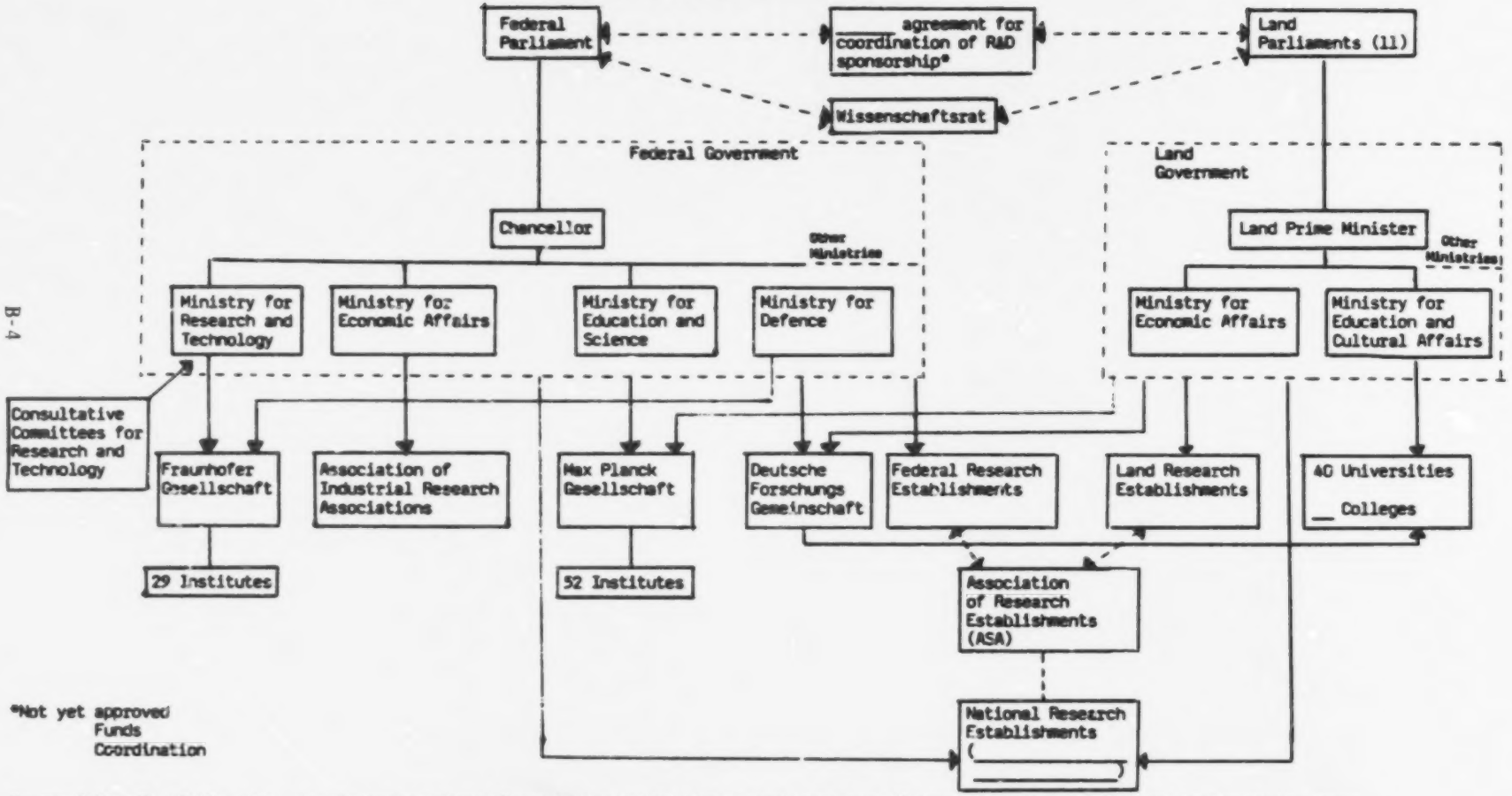
The principal federal ministries that fund biotechnology-related R&D are Research and Technology, Economic Affairs, Education and Science, and Defence. Table 1 summarizes federal research expenditures in 1985. The Bundesministerium fur Forschung und Technologie (Ministry for Research and Technology, BMFT) accounts for 55 percent of the total, with Economic Affairs, and Education and Science representing 10.2 percent and 7.9 percent, respectively. The federal government, however, accounts for only 27 percent of total R&D expenditures, with 16 percent coming from the laender governments and 56 percent from industry (3).

Basic research in biotechnology is carried out in the universities, the institutes of the Max Planck Society and certain national laboratories. University research is primarily funded by the Deutsche Forschungsgemeinschaft (German Research Society, DFG), which receives part of its funding from the Federal Ministry for Education and Science and part from the laender governments (the actual proportions depending on the program, in cases it is 50-50 or 75-25 federal to state). In addition, the Ministry provides 50 percent of the cost of new university buildings (Figure 1).

Applied research is primarily supported by the BMFT and is conducted in the institutes of the Fraunhofer Society, certain national laboratories, and a few university laboratories.

BEST COPY AVAILABLE

Figure 1.
ORGANIZATION OF THE GERMAN NATIONAL R&D SYSTEM



*Not yet approved
Funds
Coordination

Source: Arthur D. Little, Ltd., New Technology-Based Firms in the United Kingdom and the Federal Republic of Germany, distributed by Wilton House Publications Ltd., 1977, p 86.

BEST COPY AVAILABLE

Table 1.
FEDERAL R&D EXPENDITURES IN 1985

Ministry	Budget in DM ($)	% of Total
Research & Technology	7.16bn ($2.43bn)*	55.5
Education & Science	1.01bn ($343M)	7.9
Economic Affairs	1.32bn ($448M)	10.2
Defense	2.34bn ($795M)	18.2
Others	1.06bn ($360M)	8.2
TOTAL	12.89bn ($4.38bn)	100

*Average exchange rate for 1985: DM 2.9440 = $1.
M = millions, bn = billions

National Program on Applied Biology and Biotechnology (4): In order to promote the rapid development of biotechnology in West Germany, the federal government approved a new program for the period 1984-89. This program had several broad goals:

- o to stimulate basic research in the biological sciences,
- o to improve technology transfer and industrial innovation,
- o to carry out risk assessment and incorporate the results into safety regulations, and
- o to train scientists and technologists in biotechnology.

The evaluation of the strengths and weaknesses of German biotechnology are summarized in Table 2. In addition, it was determined that collaboration between universities/institutes and industry was poor, and that the environment for the creation of new, small biotechnology companies was unfavorable.

The biotechnology program has five major components: (1) institutional support, (2) creation of gene centers, (3) indirect support, (4) establishment of new, high technology companies, and (5) support of mission-oriented cooperative research.

The institutional support includes funds for the Gesellschaft fur Biotechnologische Forschung (Society for Biotechnology Research, GBF) and the German contributions to the European Molecular Biology Laboratory (EMBL) and the European Molecular Biology Conference (EMBC). The GBF is a fully integrated, biotechnology research center with projects ranging from molecular biology to downstream processing (see section on GBF).

Four gene centers have been established in Cologne, Heidelberg, Munich, and Berlin. All of these involve cooperation between research institutes, universities, and private industry, as well as funding from the BMFT and the laender governments. These gene centers involve the establishment of new research groups, as well as new facilities, such as the genetic engineering center at Munich University, an extension of the Max Planck Institute in Munich, and the Center for Molecular Biology in Heidelberg. The Berlin gene center is somewhat different, in that it involves the creation of a new institute for cell biology and was built with funds provided by the City of Berlin and the Schering company. Each gene center is intended to provide a broad range of research in molecular biology of the highest quality (Table 3). Certain government officials would prefer a greater degree of specialization at each gene center, though this has met with opposition from the scientific staff. In addition, the BMFT also provides support for research carried out at the German Cancer Research Center in Heidelberg, and at the Institute of Biotechnology at the Nuclear Research Facility in Julich.

Indirect support measures are intended to assist industry in introducing new biotechnology processes, and strengthening both interdisciplinary training and continuing education. These measures include:

Table 2.
EVALUATION OF BIOTECHNOLOGY R&D IN WEST GERMANY

Areas of Strength	Areas of Weakness	New Areas
Plant Biology	Genetic Engineering	Neurobiology
Immunology	Biology of industrially relevant microorganisms & cell lines	Enzyme design
Enzymology		
Environmental applications (particularly waste water treatment)	Bioreactor design & instrumentation	
	New biological products	

Table 3.
GENE CENTERS

Location	Participating Organizations		Budget		Research Areas
	Research Institutions	Industry	BMFT*	Industry	
Cologne	University of Cologne Max Planck Institute for Plant Breeding	Bayer	DM 16.5M ($5.6M)** 1982-86	DM 1M/yr ($339k)	Plant Biology Virology Immunology Molecular Biology
Heidelberg	University of Heidelberg German Cancer Research Center	BASF	DM 17.9M ($6.1M) 1982-85	DM 1M/yr ($339k)	Immunology Neurobiology Tumor Genetics
Munich	University of Munich: Biology, Chemistry & Medicine Departments Max Planck Institute for Biochemistry	Hoechst Wacker	DM 24.7M ($8.4M) 1984-87	Hoechst:DM 1M/yr ($339k) Wacker:DM 200k/yr ($68k)	Biosynthesis of fine chemicals & new compounds Immunology
Berlin	City of Berlin	Schering	DM 40M/10 yrs ($13.6M)	DM 40M/10 yrs ($13.6M)	Not yet decided

*Bundesministerium fur Forschung und Technologie (Ministry for Research & Technology)
**Average exchange rate for 1985: DM 2.9440 = $1.
M = millions, k = thousands

- o partial funding of industrial R&D,
- o research stipends for cooperation with foreign research institutes,
- o research stipends for young scientists,
- o funds for scientific exchanges with foreign countries, and
- o funds for returning German scientists.

In order to assist in the establishment of new biotechnology companies, the government makes available advisory services and financial support (see section on Industrial Support).

Finally, the government has selected a number of priority research topics. These are: (1) genetic engineering and microbial techniques, (2) cell culture techniques, (3) bioprocessing and enzyme techniques, (4) animal health care, (5) plant breeding and renewable resources, and (6) biological safety and substitute methods for animal experiments. Table 4 shows the Biotechnology Program budget for the period 1984-89. The single largest category is the fund for basic and applied research, with a significant portion being targeted towards risk assessment and biological safety. The next largest item is support for institutional research, i.e., GBF and EMBL.

GERMAN RESEARCH SOCIETY (DEUTSCHES FORSCHUNGSGEMEIN-SCHAFT, DFG): The DFG is an autonomous, scientific foundation, which primarily supports basic research in the universities and, to a much lesser extent, in the Max Planck Institutes. It is jointly funded by the federal and laender governments, and acts as a granting agency, with an annual budget of approximately DM 940 million ($319.3 million)*. Forty percent goes to investigator-initiated proposals, 25 percent to priority research programs, and about 35 percent to special collaborative programs (Sonderforschungsbereiche) at the universities (2). Support for biotechnology-related research is estimated to be approximately DM 200 million ($67.9 million) (5). Grants are primarily intended to cover research expenses, but do not normally include faculty salaries or overhead. The DFG also provides fellowships for young scientists. Funding decisions are made by peer review and selection is stringent.

MAX PLANCK SOCIETY (MAX PLANCK GESELLSCHAFT, MPG): The MPG is an autonomous, basic research organization. Unlike the DFG, it operates its own research institutes. It has an annual budget of approximately DM 950 million ($322.7 million), of which DM 890 million ($302.3 million) comes from the federal and laender governments. The MPG has a network of 52 institutes and a staff of 8,500 (6). Each institute concentrates on a specialized subject, and is usually located near a university. The principal institutes conducting research in biotechnology-related areas are MPI's for Biochemistry, Munich; Biophysical Research, Gottingen; Biology, Tubingen; Molecular Genetics, Berlin; Biophysics, Frankfurt; Cell Biology, Heidelberg; and Plant Breeding, Cologne.

*Average exchange rate for 1985: Deutsche marks (DM) 2.9440 = $1.

Table 4.
BUDGET FOR BIOTECHNOLOGY PROGRAM
(in millions of DM)

	1984	1985	1986	1987	1988 (proposed)	1989	Total
Institutional Support	37.4 ($12.7M)*	45.2 ($15.4M)	59.2 ($20.1M)	69.2 ($23.5M)	67.1 ($22.8M)	58.1 ($19.7M)	336.2 ($114.2M)
Gene Centers & Major Projects	14.3 ($4.86M)	19.0 ($6.45M)	24.0 ($8.2M)	26.0 ($8.83M)	32.0 ($10.87M)	37.0 ($12.56M)	152.3 ($51.7M)
Indirect Measures	2.0 ($679k)	2.0 ($679k)	15.0 ($5.09M)	27.0 ($9.17M)	35.0 ($11.88M)	40.0 ($13.58M)	121.0 ($41.1M)
Creation of Companies	0.7 ($237.7K)	2.0 ($679k)	3.2 ($1.08M)	3.8 ($1.29M)	3.8 ($1.29M)	2.5 ($849k)	16.0 (5.43M)
Mission Oriented Cooperative Projects							
Genetic Engineering, Microbial Techniques	11.3 ($3.83M)	13.0 ($4.41M)	14.0 ($4.75M)	16.8 ($5.7M)	20.4 ($6.92M)	24.6 ($8.35M)	100.1 ($34M)
Cell Culture Techniques	13.9 ($4.72M)	19.3 ($6.55M)	16.0 ($5.43M)	16.2 ($5.5M)	16.5 ($5.5M)	16.6 ($5.64M)	98.5 ($33.45M)
Bioprocessing, Enzymes	10.6 ($3.60M)	14.0 ($4.75M)	18.3 ($6.22M)	21.8 ($7.4M)	33.5 ($11.38M)	42.2 ($14.3M)	140.4 ($47.69M)
New Areas	12.4 ($4.21M)	2.3 ($781k)	2.0 ($679k)	6.5 ($2.2M)	9.2 ($3.12M)	13.0 ($4.41M)	45.4 ($15.42M)
Plant breeding, renewable resources	3.2 ($1.08M)	5.5 ($1.86M)	5.0 ($1.7M)	6.0 ($2.03M)	7.0 ($2.37M)	8.0 ($2.72M)	34.7 ($11.78M)
Biological Safety, Substitute methods for animal experiments	5.6 ($1.9M)	10.0 ($3.39M)	18.6 ($6.32M)	19.9 ($6.76M)	20.4 ($6.93M)	22.6 ($7.67M)	97.1 ($32.9M)
TOTAL	111.4 ($37.8M)	132.3 ($44.9M)	175.3 ($59.5M)	213.2 ($72.4M)	244.9 ($83.2M)	264.6 ($89.87M)	1141.7 ($387.8M)

*Average exchange rate for 1985: DM 2.9440 = $1.
M = millions, k = thousands

The MPG has a long history and its institutes are responsible for some of the best research in West Germany. Each institute has a specific program, along with generous funding and good facilities, which provides the MPI's with significant advantages. When a director retires, the particular institute and its program are reviewed. This provides an opportunity for changing the focus of the institute and directing it towards new scientific subjects. It is felt, however, that the structure of the MPG lacks the flexibility necessary to deal with the rapid pace of scientific change. Most of the authority is in the hands of the director and individual department heads. There is no adequate peer review system of research at the MPI's, leading to long-term funding without evaluation. Young investigators have few opportunities to establish their own independent research groups, and to pursue their own scientific interests. The MPG has established a number of junior groups in order to deal with this problem, but the young group leaders are on limited appointments and not on a tenure track. The MPG and the universities are complementary and represent the basis for biological research in the Federal Republic of Germany.

MINISTRY OF RESEARCH AND TECHNOLOGY (BMFT): The BMFT has the responsibility of coordinating R&D policy. The size of its budget probably makes it the single most influential science agency in West Germany. It has a central role in applied research and technology transfer, and has expanded its support for basic research in biotechnology. The BMFT does not operate its own research institutes, but funds work carried out at the universities, MPI, national laboratories and industry. Most of its responsibilities have been discussed in connection with the Biotechnology Program (see Table 4).

INDUSTRIAL SUPPORT

The federal government has pursued policies to assist in the creation of new companies. As part of its biotechnology program, the following measures have been taken:

Stimulation of the Biotechnology Industry: The objective is to introduce new products and processes into the industrial sector. Actual commercialization is left to the companies themselves. In order to qualify for support, the projects have to be in one of the following areas:

- o cell culture techniques;
- o genetic engineering;
- o processes with tissue culture, genetically engineered microorganisms and plant protection;
- o enzymatic processes in health care and food production;
- o equipment development for cell culture and genetic engineering; and
- o bioreactors, as well as measurement and control technology.

The grant can cover up to 40 percent of the cost of the project, to include R&D personnel costs, investment costs, and R&D costs from third parties and consulting services. These grants may not exceed DM 600,000 ($203,800) per company (4).

Support for New Biotechnology Companies: The federal government is collaborating with banks and risk capital organizations to create new entrepreneurial companies. The selected technologies are the same as those mentioned in the preceding section. The following assistance is provided (4):

Phase I -- up to 90 percent of the cost of advisory services, including initial costs, search for external financing, technical counseling, and market studies.

Phase II -- up to 75 percent of the cost of development (until a marketable prototype is ready).

Phase III -- guarantee of up to 80 percent of bank credit for production and marketing.

In addition, the BMFT and industry have created a Foundation for Biological Chemistry, which funds the movement of scientists between academic laboratories and industry. The Foundation has a budget of DM 30 million ($10.2 million) for the period 1983-88. In addition to these specific programs for biotechnology, the federal government has three other general programs:

(1) the European Recovery Program, which provides loans for starting new companies;

(2) the Paid-In Capital Creation Program, which provides subsidies for interest rates; and

(3) supplementary programs that provide loans to new companies. Individual lender and local governments also have programs of their own in order to attract high technology industries.

The federal government has proposed new legislation governing investment companies which acquire equity in small and medium-sized companies while selling their own shares on the stock market. Hopefully, this will allow individual investors to become involved in smaller, innovative firms. The bill will require investing companies to have a minimum capital of DM 2 million ($679,000), that they invest in a minimum of 10 companies, and after 8 years they must offer a minimum of 75 percent of their capital to the public (8).

Biotechnology Regulation: The government established safety guidelines in 1978, based on those of the National Institutes of Health (NIH) in the U.S. The guidelines are administered by the BMFT's Committee for Biological Safety. A parliamentary commission is due to publish an assessment of genetic engineering, and make recommendations on any necessary new legislation (8). It had been the government's intention that industry should be subject to voluntary compliance of the existing guidelines. Strong criticism from the environmentalist party, the Greens, has now forced the government to introduce a set of revised guidelines that will be binding on industrial processes (9).

III. UNIVERSITIES AND RESEARCH INSTITUTES

West Germany has a solid research base in the biological sciences, centered around its universities and the Max Planck Institutes. Some of the most important have been organized into gene centers in Cologne, Munich, Heidelberg, and Berlin. A number of institutes carry out applied research, such as the privately owned Battelle Institute, the government funded Institute of Biotechnology at the Nuclear Research Center, Julich, and the GBF. The institutions visited include the Institute of Genetics at the University of Cologne, the Max Planck Institute for Plant Breeding, the Max Planck Institute for Biochemistry, the GBF, the Institute of Biotechnology at the Nuclear Research Center (IBT), Julich, and the Battelle Institute.

(a) Financial support: Research in the universities is jointly funded by the federal and laender governments. The laender pay for faculty salaries, administrative costs, and infrastructure, though this is generally considered to be inadequate. The costs of new buildings are jointly shared by the laender and the Ministry of Education and Science. Research costs are usually covered by grants from the DFG and the BMFT. The Max Planck Institutes are supported by the MPG, and can apply for grants from the DFG and BMFT. The biotechnology institutes (IBT and GBF) were 90 percent funded by the BMFT and 10 percent by the laender government. The IBT is, however, now being fully supported by the government of North Rhine-Westphalia. The Battelle Institute is a private, nonprofit organization that conducts research on contract to the government or industry.

Though university funding and DFG budgets have remained fairly constant, the Biotechnology Program has resulted in an increase in the funds available from the BMFT. In the case of the Cologne gene center, it is stated that total funding increased very significantly (including industrial contributions) (10). The Max Planck Institutes and the GBF have also benefited from the Program. One limiting factor in the case of the universities, is that the number of faculty positions has remained nearly fixed, as has investment in the infrastructure. Nevertheless, real R&D spending on biotechnology has grown, and it is questionable whether larger sums could be used effectively in the absence of changes in the research system.

(b) Scientific Research: Overall, German research in the biological sciences covers a broad number of areas, and is outstanding in specific areas. (Table 5 summarizes the research activities at the institutes visited). The two institutes involved in the Cologne gene center were visited, as well as one of those participating in the Munich gene center. They reflect German strength in molecular and cell biology of animal viruses and plant systems, immunology, protein chemistry, and structural biology. Underpinning this is a long tradition in biochemistry and enzymology.

It is evident that the gene centers at Cologne and Munich were established around existing institutions and facilities. To a great extent, the gene center concept provides a structure for the expansion of research in specified directions. The execution is complicated by the difference in the nature of the participating institutions (universities = research + teaching, direct

Table 5.
RESEARCH CENTERS VISITED

	Institute of Genetics University of Cologne[1]	Max Planck Institute for Plant Breeding[2]	Max Planck Institute for Biochemistry[3]	Institute of Biotechnology, Nuclear Research Center, Julich[4]	Society for Biotechnology Research (GBF)[5]
Principal Research Themes	Transposons in E.coli & plants Control of gene expression in adenovirus and baculovirus Protein chemistry Control of gene expression in immunological systems Lymphokines DNA-protein interaction Alzheimer's Disease	Mechanisms of resistance to pathogens & UV in plants Construction of minichromosomes Plant genes & factors involved in development Regulation of light, heat & tissue-regulated genes Development of plant vector systems Genetics & breeding & yield physiology of barley & potato	Gene expression in archebacteria, eubacteria & eukaryotes Structure of biological membranes Signal transmission in membranes Peptide chemistry -hormones -hemoglobin Electron microscopy X-ray crystallography Virus research & hoof & mouth disease Developmental genetics of slime mold & insects Molecular biology of phages	Optimization of processing technology Characterization & application of cellulases & ligninases Microbiology of anaerobic fermentation Waste water treatment with bacteria or bacteria-algae mixed cultures	Biologically active metabolites from myxobacteria Translation control in E.coli Control of expression of IFN Immunomodulators (IL-2) & cell markers DNA & Peptide synthesis Applications of Enzymes to bioprocessing Plant cell culture Bioreactors for animal cells Computer Control, fermentation & downstream processing Culture Collection

1. Doerfler, Professor Walter, Institute of Genetics, University of Cologne, personal communication, June 1985.
2. Salamini, Professor F., Institute for Plant Breeding, Cologne, personal communication, June 1985.
3. Hofschneider, Professor P.H., Institute for Biochemistry, Munich, personal communication, September 1986.
4. Wandrey, Professor C., Biotechnology Research Institute, Julich, personal communication, June 1985.
5. Klein, Professor J., Biotechnology Research Institute, Braunschweig, personal communication, September 1986.

laender funding; MPI = pure research, funding through MPG), and by physical locations (e.g., the University of Cologne is in the city while the MPI for Plant Breeding is in the suburbs. The same is true of the University of Munich, with the MPI for Biochemistry located in Martinsried, outside of Munich). In both cases, there is some interaction between groups at the different institutions, but this is not considered optimal. It remains to be seen how the gene centers will deal with these problems.

One of the goals of the government has been to promote technology transfer, to apply biotechnology to production and processing. West Germany has pioneered in the creation of biotechnology institutes that integrate basic research with fermentation and downstream processing technologies. (Table 5 shows the research activities at the IBT and GBF.) The overlap in a number of research areas, and a critical review of groups at the GBF, led to the recommendation that the IBT be closed, and its principal programs transferred to the GBF (11). This was not accepted by the IBT, and it has continued its operations with funding from the laender of North Rhine-Westphalia. The BGF has also been undergoing reorganization under a new director.

The Department of Biology at the Battelle Institute primarily conducts routine toxicology tests (12). It has a new biotechnology unit that does research on the following areas:

- o waste water treatment,
- o development of a vector for use in industrial production,
- o development of a system for immobilizing enzymes, and
- o enzyme engineering.

Research is funded through contracts, primarily from the federal government. Many of the biotechnology activities are directed towards industrial applications, in competition with the IBT and the GBF.

(c) University/Institute-Industry Interactions: This is probably the single weakest link in the development of biotechnology in West Germany. There was little evidence of close collaboration with industry in the three basic research institutes visited. As indicated previously, there was significant financial support from industry for expansion of biotechnology-related activities, and there is the occasional assignment of an industrial scientist to an academic laboratory. It is the stated purpose of the IBT and the GBF to develop close ties with industry. At the IBT, they have worked closely with Dechema on the scale-up of laboratory experiments, with Schott on membrane reactors, and has sold its water treatment technology to two companies for a total of DM 600,000 ($203,800). The GBF has increased the number of its agreements with companies. During 1985, it had contacts with 45 companies, leading to 7 licensing contracts and 3 contracts involving technology transfer (13). It is estimated that approximately 25 percent of the research is industry-related, though the income from the private sector is only around DM 2 million ($679,000) per year, or 5 percent of the total budget (14).

A large proportion of biological research is concentrated at certain elite universities and at the MPI. Unlike the technical universities that have always had ties with industry, the universities and the institutes have remained aloof from industrial activities. That this attitude persists is demonstrated by the following:

(1) Very few of the most prominent German biological researchers have joined industry. One exception was the creation of Progen Biotechnik by four scientists from the University of Heidelberg and the German Cancer Research Center. None of the four has resigned their academic positions.

(2) Discussions with graduate students revealed the widespread belief that industry would not provide them with sufficient job opportunities.

(3) Of 17 young scientists at the Institute of Genetics in the period 1974-84, two went into industry (10). The strong orientation towards pure research and the lack of mobility between the academic and industrial worlds remain major obstacles to technology transfer, though this is likely to change.

(d) Staffing: The German system of higher education provides an adequate supply of well qualified graduates, and has successfully improved its teaching of modern biology. There are, however, still some substantial gaps in certain subjects, such as bacterial physiology, plant biochemistry and bioengineering.

The most serious problem is the lack of independent positions for young scientists. The rapid expansion of the universities in the 1970's has resulted in an unusually large number of faculty members and researchers in their 40's or 50's, providing few opportunities for new people. At the same time, labor laws effectively provide tenure after 5 years, which acts as a deterrent in establishing new research groups for specific projects. The DFG has created the Heisenberg Program in order to provide 5-year positions for young investigators, in an attempt to alleviate this problem. It is hoped that the creation of 200 positions at the gene centers will also help.

(e) Education: University and graduate education in West Germany is of good quality, but the duration of training is long. Perhaps even more serious, is the age at which a scientist can expect to arrive at an independent position. The average student is likely to receive his gymnasium (high school) degree at age 19-20. Males then serve 15 months in the military or 18 months in a substitute social service*, and will be 21-22 when admitted to university. The diploma degree takes 5-6 years, followed by 3 years of graduate training for the Ph.D. So, the average Ph.D. will be 28-30 years old, and if he spends 3 years in postdoctoral training in Germany or abroad, he is likely to be 33 years old when he takes his first position (usually as

*Beginning in 1989, these periods will be extended to 18 and 24 months, respectively.

an assistant in a university). This first position is normally dependent upon a professor or department head, and lasts 5 years. It is, therefore, not unusual for a scientist to be 38 years old when he moves into his first independent position. This is considerably older than his American counterpart, who is likely to be in his early 30's. It is suspected that the lack of positions for young investigators, as well as the long apprenticeship, may account for some of the conservatism of the German R&D system and the lack of entrepreneurial spirit.

IV. INDUSTRY

Germany has a powerful industrial base in biotechnology, centered around major chemical and pharmaceutical multinational corporations. While there are also a large number of medium-sized companies in specialty chemicals, food, and instrumentation, there are only a small number of new biotechnology companies. During the course of the study, visits were made to Bayer, Hoechst, Boehringer-Ingelheim, Merck, Gen-Bio-Tec, and Garching Instruments.

BAYER is the largest of the German chemical groups and its operations are summarized in Table 6. Fifty-five percent of sales in 1985 were in Europe and 23 percent in North America, with foreign sales accounting for 80 percent of the total. Sixty-one percent of its R&D operations are in West Germany and 27 percent in the U.S. (15).

Bayer, like the other German chemical companies, has been extremely profitable during the last 2 years. While pharmaceuticals accounted for 15 percent of sales in 1985, and agrochemicals for another 15 percent, these sectors account for 51 percent of R&D expenditures, indicating a shift in future business priorities. Biotechnology research accounts for DM 200 million ($67.9 million) and is seen as a long-term investment with the most immediate impact in pharmaceuticals. Until recently, technology transfer went from Germany to the U.S., primarily in the form of new processes. The expansion of the North American market coincides with the shift into pharmaceuticals, and is symbolized by the purchase of the Bayer trademark (lost during World War II) for $25 million. Bayer USA has three principal operations: Mobay Chemicals (paints, agrochemicals); Miles (pharmaceuticals, OTC products, enzymes); and Helena (chemicals).

Biotechnology R&D has been divided along geographical lines. Wuppertal concentrates on cardiovascular agents, beta blockers, anti-hypertensive drugs, antibacterial agents, and diabetes therapy. Bayer also supports the Cologne gene center and its work in plant biology. Miles, in the U.S., has Cutter Labs, which is responsible for blood products and monoclonal antibodies. Its Ames division is involved in the production of diagnostics. A new pharmaceutical center is being established in West Haven, CT, at a cost of $35 million. This will include a new biotechnology company, Molecular Diagnostics, in which Bayer holds 60 percent of the equity, and will be responsible for clinical testing for FDA approval, and development of new, natural drugs using recombinant DNA (rDNA) technology. Though Miles is the world's third largest producer of industrial enzymes, this has not been a very profitable operation.

Table 6.
COMPANIES VISITED

	Bayer	Hoechst	Merck	Boehringer-Ingelheim
1985 Sales	DM 45.926bn ($15.6bn)*	DM 42.722bn ($14.511bn)	DM 3.286bn ($1.12bn)	DM 4.528bn ($1.538bn)
Change from previous year	+6.7%	+3.1%	+9.2%	+10%
1985 Profits	DM 1.436bn ($487.7M)	DM 1.468bn ($498.6M)	DM 298.8M ($101.5M)	DM 127M ($43.13M)
Change from previous year	+22.3%	+8.6%	+7%	+5%
Business	Inorganic chemicals 19% Health Care 15% Agrochemicals 15% Agfa-Gevaert 16% Polymers 8% Organic chemicals & Dyes 14% Others 3%	Pharmaceuticals 16% Plastics 10% Varnishes 10% Textiles 10% Agriculture 7% Inorganic Chemicals 6% Organic Chemicals 5% Pigments 5% Plastic Film 4% Detergents 4% Industrial gases 4% Information technology 4% Plant engineering 2% Other activities & joint ventures 13%	Pharmaceuticals 38% Chemicals 54% Plant Protection 5% Others 3%	Pharmaceuticals 85% Industrial & Consumer products 15%
R&D Expenditures	DM 2.134bn ($724.9M)	DM 2.083bn ($707.5M)	DM 208.3M ($70.75M)	DM 630M ($214M)
Change from previous year	+9.1%	+15%	+14.2%	+12%
R&D Areas	Anti-hypertension Anti-rheumatism Plasma & blood products Therapeutic uses of monoclonal antibodies Herbicide resistance in plants Vaccine for hoof & mouth disease	Arteriosclerosis treatment Anti-tumor drugs Chronic bacterial infections Progressive diseases Immunology Biological pesticides Plant physiology	Anti-hypertension Coronary heart disease Pain relief Neurological agents HPLC Biological separations Diagnostics	Alpha & Beta Interferon TPA Drug delivery systems Cancer research
Agreements	R&D contract & rights to Factor VIII from Genentech Acquisition of Molecular Diagnostics Acquisition of Biolac	Licensing University Patents Inc. Joint R&D with Techamerica Funding department at Massachusetts General Hospital Joint R&D with Immunex Licensing with Electronucleonics	Equity in EM Diagnostics	Acquisition of 4.5% of Genentech Creation with Genentech of research institute in Vienna Establishment of Genentech Canada Joint development with Alza

*Average exchange rate for 1985: DM 2.9440 = $1.
Source: Each company's 1985 annual report.
M = millions, bn = billions

BEST COPY AVAILABLE

Bayer is a tightly managed, conservative organization. Its philosophy is to be product related (along traditional lines), to gradually introduce new technologies into established businesses, and to minimize the cost of investment in new physical plant. It finds biotechnology an expensive and highly risky business, but not one it can afford to stay out of. Its biotechnology strategy is to buy and license technologies, and proceed with acquisition of companies with established biotechnology processes and products. This strategy is directed, in large part, towards the U.S., and Bayer has raised a record DM 1.1 billion ($373.6 million) in the German capital market to implement it. Table 6 shows some of its major U.S. activities. In comparison with its principal European competitors, these activities are relatively minor.

HOECHST is another of the three major German chemical groups. A summary of its activities appears in Table 6. Seventy-five percent of total sales in 1985 was outside of Germany. Of this amount, 15 percent was in North America. While pharmaceuticals accounted for only 16 percent of total sales, they represent a major area for business expansion and 47 percent of total R&D expenditures are now in that sector. R&D is conducted in large research centers in Germany, France, the U.S., Japan, and the U.K. (17).

Hoechst's three priorities in the biological area are: (1) the isolation and characterization of new products, especially in the medical field, (2) the study of pathogenesis, and (3) research on plant physiology. Hoechst has been skeptical of biotechnology's ability to generate profitable, new products in the short-term. After some hesitation, however, several highly visible moves have been made (18):

(1) An agreement, in 1980, with Massachusetts General Hospital to fund a genetics department at a cost of $50 million, created a political furor that contributed to the establishment of the West German Biotechnology Program.

(2) Funding of the gene center in Munich at the rate of DM 1 million ($339,600) per year.

(3) Behringwerke (in West Germany) and Roussel-Uclaf (in France) are two Hoechst companies that are involved in the pharmaceutical sector. Behringwerke is developing blood factors (in collaboration with U.S. biotechnology companies), and total diagnostic systems including laboratory equipment. Roussel-Uclaf has a major research program on drug design, and is actively collaborating with the Centre National de la Recherche Scientifique (CNRS) of France (see Chapter on France).

(4) Hoechst has established a new company, as a joint venture, with Polaroid, for the development of new diagnostic systems.

Hoechst is building a major production facility for the manufacture of genetically engineered human insulin, which should be ready by early 1987. This same facility will be used for other rDNA products, including interferon.

In addition to expanding its operations in the U.S., it is believed that Hoechst also intends to build up its biotechnology portfolio there. It is currently raising an additional $390 million in capital, and it is assumed that much of this will be targeted for acquisitions in the U.S., where it has already invested $1 billion.

MERCK is one of the medium-sized German chemical groups. Approximately half of its sales are in Europe, with foreign sales accounting for almost three-quarters of total sales. The chemicals sector is still the largest (Table 6) and increased by 13 percent in 1985, while pharmaceuticals only rose by 7.7 percent (19).

Merck's biotechnology-related activities are in the Pharmaceuticals Division, which also accounts for 60 percent of its R&D expenditures. Merck has taken advantage of its long tradition in the production of analytical-grade reagents to develop HPLC systems, both for diagnostic purposes and also for large-scale separation of biological molecules. Merck is collaborating with Eppendorf in the production of integrated diagnostic systems, and in the long-term development of biosensors. Diagnostics activities are being expanded in the direction of immunological techniques, medical microbiology, and cell analysis.

Merck's first use of new biotechnological processes has been in the introduction of enzymatic steps in the synthesis of steroids. It is conducting research into large-scale enzyme purification, hoping to expand the use of enzymes in chemical synthesis.

In collaboration with two German companies, Rohm and Gruenenthal, and the University of Darmstadt, Merck has established a gene center with the BMFT funding 50 percent of the projects (20). There are currently seven projects under way. It was the only large company visited which felt that the collaboration with universities was both productive and cost effective. They are also collaborating with the University of Heidelberg, the GBF, and the Institute of Biotechnology at the ETH/Zurich.

Merck has been relatively slow in penetrating the U.S. and Japanese markets, but is beginning to develop its diagnostics business in the U.S. through its partially owned subsidiary, EM Diagnostics.

BOEHRINGER-INGELHEIM is one of the larger German pharmaceutical companies, with a large export market that accounts for 79 percent of its sales (see Table 6). The U.S. is the most important market, and with Canada, represented 25 percent of total sales in 1985, an increase of 21 percent over 1984. Japan is the second most important market (21).

Boehringer-Ingelheim has established production facilities in each major market. It has been one of the most aggressive German companies in expanding its biotechnology activities. Some of the most recent moves have been at its own subsidiaries, or in collaboration with foreign companies (22):

(1) Bender & Co., Vienna: production of alpha-interferon, which is presently being marketed;

(2) Dr. Karl Thomae, Biberach: a new facility for the production of genetically engineered tissue plasminogen activator (TPA) is being built;

(3) Establishment of strong ties with Genentech (see Table 6), including the creation of a new Oncology Research Center in Vienna, and

(4) Development of new drug delivery systems with Alza.

In addition to the construction of biotechnology facilities in Europe, the company is adding an extension to its research facilities in Connecticut. All of these R&D projects are consistent with their traditional product lines: interferon (treatment of viral diseases), TPA (treatment of cardiovascular conditions) and tumor necrosis factor (TNF, cancer treatment).

GARCHING INSTRUMENTS is a company established by the Max Planck Society in 1971, to commercialize the work done in its institutes. It identifies industrially relevant projects and licenses the results to industry. When a private company is interested in specific research at one of the institutes, it can deal directly with the institute and fund the project through a grant. Garching's annual income was DM 3 million ($1.02 million) in 1985. Thirty-three percent of the royalties were paid to the individual(s) responsible for the research (23).

Approximately 50 percent of Garching Instrument's agreements are in the area of instrumentation and special materials. The other 50 percent are in the biological area (mainly monoclonal antibodies and plant breeding). German companies account for 50 percent of these agreements, with foreign companies making up the other 50 percent. U.S. companies are the most active in arranging deals with Garching. It was felt that, in general, German companies are more conservative and less willing to enter into arrangements with outside organizations.

GEN-BIO-TEC: The number of new biotechnology firms in West Germany is small, estimated between 6 and 10. Gen-Bio-Tec was established in 1983 by a young microbiologist from the University of Heidelberg. The capital for the firm was obtained from the following sources (24):

-DM 500,000 ($169,800) from the land of Baden-Wuttenmberg and local banks;
-DM 900,000 ($305,700) from the BFG, a venture capital organization;
-DM 1 million ($339,600) grant from BMFT; and
-DM 1.6 million ($543,400) credit from commercial bank (80 percent guaranteed by the government).

Total capital: DM 4 million ($1.36 million). In addition, space was provided at a token price by the city of Heidelberg.

The strategy of Gen-Bio-Tec is to establish joint ventures with small and medium-sized pharmaceutical companies in West Germany, with Gen-Bio-Tec being responsible for R&D and the larger partner for production and marketing. Gen-Bio-Tec also retains the rights to license the products to companies outside of Germany. The original plan was to develop therapeutic proteins and

carry out contract R&D. Its first product is genetically engineered hirudin, an anticoagulant. This is being followed by protein A fragments, which are being used for IGG isolation.

It is generally acknowledged that the establishment of new, high technology companies in West Germany is a difficult endeavor. For Gen-Bio-Tec, the most serious problems have been:

- o lack of capital and financing,
- o cash flow difficulties,
- o conservative attitudes towards contract R&D,
- o inadequate market analyses, and
- o international competition in contract R&D.

Annual turnover is DM 1 million ($339,600), which is not sufficient to maintain an adequate cash flow. It is apparent that the German industrial establishment is not particularly receptive to the idea of contract R&D to a small new firm. In addition, Gen-Bio-Tec became a "cause celebre" when it neglected to notify the Federal Office for Biological Safety of its use of genetic engineering methods in the production of hirudin. This resulted in a campaign by the Green Party that has forced the government to change its proposed policy for regulation of biotechnology in industry (see Government Policy).

VENTURE CAPITAL

The availability of venture capital for new, high technology firms is a major political and economic issue in West Germany. Following the second oil crisis in 1973, there was a wave of bankruptcies blamed on the undercapitalization of many German firms. As the German economy has been restructuring itself away from traditional, heavy industry into more modern technical and service sectors, there has been intense debate about the international competitiveness of German industry. This has resulted in increased support for expanding the pool of venture capital and promoting the creation of new, high technology companies (25).

In 1975, the Deutsche Wagnisfinanzierungs Gesellschaft (risk investment society) was set up, with the participation of 29 banks. Its operations were slow and cumbersome, and it did not have a significant impact on innovative new firms. It was reorganized in 1984. The Kohl government is much more enthusiastic about entrepreneurship and new businesses, and has acted to improve the environment for such activities. It is now estimated that the total amount of European venture capital is $5.6 billion. West Germany is fourth in terms of availability of venture capital, with 9 percent of the total (26). Thirty venture capital organizations are now in existence, with a total capitalization of DM 800 million ($271.7 million). Only DM 100 million ($33.9 million), however, have been invested to date (27). One of the more successful of these organizations is Techno Venture Management in Munich, which has benefited from the expertise of its U.S. and U.K. partners.

Though the prevalent view is that the lack of new, high technology companies is due to the unavailability of venture capital, a number of

observers believe that other factors are equally important:

(1) Cultural: the high social value placed on security, and the strong negative consequences of failure.

(2) Tax policies: these are generally adverse to capital formation in companies, and to employee participation.

(3) Stock market: high cost and structural obstacles to going public.

(4) Experience in venture capital: lack of financial and technical expertise in evaluating new companies.

(5) Capitalization: the average company only holds 18.5 percent of its own equity.

(6) Low emphasis on high technology: an average 200,000 new businesses are established annually, but only one percent are in the high technology sector.

The present government has moved aggressively to assist new companies, primarily by expanding the base of venture capital (see Government Policy). It is important, however, to realize that the role of the government is limited, and that the creation of new companies cannot be viewed simply in the context of national economic objectives.

INDUSTRIAL OVERVIEW

West Germany has a strong industrial base in the chemical and pharmaceutical sectors. Industry invests heavily in R&D (58 percent of the national R&D expenditures) and is particularly well disposed to technological innovation. Historically, the universities and industry have accepted a sharp definition of their individual roles in research: basic research in the universities and industrially relevant R&D in the company laboratories. Industry has also concentrated all of its research in-house, and has been reluctant to contract out research or enter into joint ventures.

The major German chemical and pharmaceutical companies have posted major profits recently, but have realized the necessity to move away from bulk chemicals and into high value-added products such as pharmaceuticals. In so doing, they have had to grapple with two major issues. First, is the skepticism in corporate board rooms about the future impact of biotechnology. The long tradition in chemistry, and the massive investments in chemical processing, had resulted in a conservative attitude toward biotechnology during the 1970's. There were also serious concerns about biological safety and opposition from the environmental movement. The first major break was Hoechst's agreement with Massachusetts General Hospital in 1980. This move was considered an important, well thought-out step to promote government and industrial support for molecular biology. The political impact was major, though the choice of the program has been widely criticized. This was followed by industrial support for the BMFT's Biotechnology Program. The second major issue is the expansion into the U.S. market (much was lost

through confiscation during World War II), an expensive and time-consuming process. The major companies have increased their biotechnology activities, as evidenced by the construction of production facilities for genetically engineered products by Hoechst, Boehringer-Ingelheim, and Bayer. Licensing agreements with U.S. biotechnology companies, and the strategic alliance between Boehringer-Ingelheim and Genentech, are harbingers of the future.

The major weakness in the German industrial landscape is technology transfer. Both the federal and laender governments have exerted themselves in its promotion, but academic scientists, corporate executives, government officials, and entrepreneurial industrialists agree that it will be a long and slow process, requiring major structural and cultural changes. The opportunities for successful creation of new companies are extremely limited, and it is very doubtful that this will be an important mechanism for technology transfer. It may well be that a short-term solution may involve greater decentralization in the large companies and more willingness to contract R&D to outside organizations.

V. CONCLUSION

Intrinsically, West Germany is in a most favorable position for the industrial development of biotechnology. Its basic research establishment is the best funded in Europe, facilities are first-class, and research covers a broad spectrum of biological subjects. In addition, West Germany has always had a consensus within its government-industrial establishment to support basic research. In industry, almost all biotechnology activities are concentrated in a number of large, highly profitable, technologically advanced chemical and pharmaceutical companies.

The basic research establishment was somewhat slow in moving into genetic engineering, cell fusion and the other new biological concepts. The corporate sector was even more hesitant, and only recently has begun to expand its biotechnology activities. Government and industry leaders have been concerned about the missed opportunities in the computer and electronic industries, and have focused their energies on the issues of technology transfer and new company formation. The Kohl government has been particularly enthusiastic about promoting the development of high technology industries, and has acted by providing direct support and trying to create a more favorable environment for entrepreneurial activities. It has to be emphasized, that unlike some of the other European countries, the laender and local governments play an important role both politically and financially.

In biotechnology, the federal government's principal initiative has been its Biotechnology Program. One of the objectives of the Program has been to increase basic research in general, and in weak subject areas, specifically. Most participants believe that the results are generally favorable. There are structural problems that are not easily amenable to funding solutions. Those most frequently mentioned are:

- the long delay before a young scientist acquires an independent position and the scarcity of such positions;

- o the rigid departmental structures that inhibit interdisciplinary projects; and,

- o the lack of close university-industry interactions.

The other principal objective of the Program is to promote technology transfer and the establishment of new companies. The federal government has experimented with a wide variety of measures (see section on Biotechnology Program), both direct and indirect. It is too early to determine the effectiveness of such measures, but there is little discussion of an evaluation mechanism or of standards for success or failure. There has already been criticism of the standards of scientific excellence used for the more applied projects sponsored by the BMFT and the work carried out at the IBT and the GBF (two major centers of biotechnology research). It is felt that these were not of the same level as those used by the DFG or the MPG.

Industry has responded favorably to the Biotechnology Program, and to the active role played by Minister Riesenhuber of the BMFT. Most of the large companies, though, feel it has had very little impact on their own activities. After a slow start, they have begun to develop their own strategies in biotechnology, mainly by integrating these techniques into current operations. In agreements with U.S. companies, they have preferred to acquire concrete products and processes, and/or the companies involved. One senses that this is done more out of fear of being left behind than out of a spirit of excitement at the possibilities in the future. The number of new biotechnology companies is small, and the chances for commercial success seem slim indeed.

The major German companies, particularly those in chemicals, have been highly profitable during the past few years. Their large cash reserves, expansion into the U.S. market, and the fall of the dollar, have made U.S. acquisitions increasingly attractive. The purchase of Inmont by BASF for $1 billion has recently been dwarfed by Hoechst's offer of $2.85 billion for Celanese (28). It would not be surprising if the same strategy was applied to U.S. biotechnology companies with tangible assets and product lines.

Finally, both the Kohl government and industry believe in promoting a free market environment and reducing government intervention. The dilemma is that taking advantage of the rapid pace of scientific research requires changes in the structure of the research establishment and in the adoption of new technologies by industry. The past record shows that neither academia, nor industry, are likely to do this on their own.

ACKNOWLEDGMENTS

Waltraud Enzmann, Commercial Specialist, Foreign Commercial Service, American Consulate, Stuttgart.

Walter Hage, Commercial Counselor, American Embassy, Bonn.

REFERENCES

1. 1986 Economic Trends in the Federal Republic of Germany: Implications for U.S. Business, United States Embassy, Bonn, Germany, January 1986.

2. Report on Science and Technology in the FRG, December 1984.

3. Dusseldorf VDI Nachrichten, January 25, 1985.

4. Angewandte Biologie und Biotechnologie, Programm der Bundesregierung, 1983.

5. Gruenhagen, Dr. Frank, German Research Foundation, personal communication, June 1985.

6. Support and Structure of the Basic Research Establishment in West Germany, American Embassy, Bonn, December 16, 1980.

7. Government Programs to Support and Promote New Businesses, American Embassy, Bonn, May 7, 1985.

8. Financial Times, London, June 4, 1985.

9. Science, April 4, 1986.

10. Doerfler, Professor Walter, Institute of Genetics, University of Cologne, personal communication, June 1985.

11. Wandrey, Professor C., Biotechnology Research Institute, Julich, personal communication, June 1985.

12. Frevert, Dr. Jurgen, Battelle Institute, Frankfurt, personal communication, September 1985.

13. GBF Annual Report, 1985.

14. Klein, Professor J., Biotechnology Research Institute, Braunschweig, personal communication, September 1986.

15. Bayer Annual Report, 1985.

16. Buechel, Professor K.H., Bayer, personal communication, September 1986.

17. Hoechst Annual Report, 1985.

18. von Wasiliewski, Professor E., Hoechst, personal communication, September 1985.

19. Merck Annual Report, 1985.

20. von Kessel, Dr. K., Merck, personal communication, September 1986.

21. Boehringer-Ingelheim Annual Report, 1985.

22. Struck, Dr. Carl J., Boehringer-Ingelheim, personal communication, September 1986.

23. Herbeck, Dr. Reiner, Garching Instruments, personal communication, September 1986.

24. Sommer, Dr. Reinhold, Gen-Bio-Tec, personal communication, September 1986.

25. Frankfurter Zeitung/Blick Durch Die Wirtschaft, September 30, 1985.

26. Financial Times, London, July 19, 1986.

27. Financial Times, London, December 3, 1985.

28. The Economist, November 8, 1986.

.081

APPENDIX

INSTITUTIONS AND INDIVIDUALS VISITED

Government

Deutsche Forschungsgemeinschaft (German Research Foundation): Dr. Frank Gruenhagen, M.A.

Bundesministerium fuer Forschung und Technologie (Federal Ministry for Research and Technology): Dr. K. Bauer, Director of Biotechnology; Dr. P. Lange.

Universities and Research Institutes

Institute of Genetics, University of Cologne: Professor Walter Doerfler.

Max Planck Institute for Plant Breeding, Cologne: Professor F. Salamini, Department Head.

Gesellschaft fuer Biotechnologische Forschung, Braunschweig: Professor Dr. Joachim Klein, Scientific Director; Dr. Irene Wagner-Dobler, Assistant to the Director.

Battelle Institute, Frankfurt: Dr. Jurgen Frevert, Biochemistry Department; Dr. Martin Mieschendahl, Biotechnology Department.

Industry

Hoechst: Professor Dr. E. von Wasiliewski, Director of Research, Pharmaceutical Division; Dr. Hans-Dieter Sumn.

Garching Instruments: Dr. Reiner Herbeck.

Bayer: Professor Karl Heinz Beuchel, Member of the Management Board in Charge of R&D; Dr. Heinz-Georg Nordmann, Coordinator for R&D; Dr. Ernst Truscheit, Director of Institute of Biochemistry and Coordinator for Pharmaceutical R&D.

Gen-Bio-Tec: Dr. Reinhold Sommer, Owner.

Boehringer-Ingelheim: Dr. Carl J. Struck, Project Manager, Biochemicals, Chemical Division.

Merck: Dr. Kurt von Kessel, Member of the Board of Management; Dr. Hermann Lang, Leader of Biochemistry Research.

.382

SECTION C

BIOTECHNOLOGY IN ITALY

SUMMARY

At present, Italy is much more of a market for biotechnology than it is an active competitor. Though research funding appears adequate, there is a serious lack of coherent government policy and a shortage of major research centers. Three major Italian industrial groups have become involved in biotechnology, but their R&D efforts are off to a late start. Traditionally, they have coped by purchasing basic reagents, licensing products and making joint ventures with foreign partners.

I. INTRODUCTION

The Italian economy had a period of recovery that began in the second half of 1983 and continued through the first half of 1985. The level of economic activity appeared to have flattened out during the second half of 1985, with inflation declining to about 6 percent in early 1986 (1). Economic growth has been stimulated by an increase in exports, principally in consumer goods. The U.S. represents Italy's third most important trading partner after Germany and France.

Italy has been an increasingly good market for American products particularly in sectors associated with high technology such as computer hardware and software, and laboratory and medical instrumentation. In the industrial sectors related to biotechnology, three major industrial groups (ENI, Montedison and Fiat) have initiated significant R&D efforts concentrating in diagnostic and pharmaceutical products. Unlike most of its European neighbors, the Italian government has been slow in promoting biotechnology and applying it for industrial innovation. This governmental attitude has only begun to change recently.

(Unfortunately, time constraints, the unexpected cancellation of some meetings, and a sparsity of published material has limited this study of biotechnology in Italy. Eight meetings were held, primarily with key persons in industry and research, and there was participation in an International Symposium on Radioimmunoassays and DNA Probes held in Florence.)

II. GOVERNMENT POLICY

The Italian government has been widely criticized for its lack of initiative in supporting basic research and in promoting better interactions between research laboratories and industry, although recently several steps have been taken to remedy this. Unlike most of its European neighbors, Italy lacks a ministry that has strong authority over science and technology. The Minister for Scientific Research is a minister without portfolio whose role is to coordinate the scientific activities of the various ministries and to obtain funding for new scientific programs. However, he does not possess an administrative structure nor a fixed budget, and thus has limited influence.

The single most important organization in Italian science is the Consiglio Nazionale delle Ricerche (CNR, the National Research Council). The Ministries of Health and Education, and the National Organization for Alternative Energies also fund research in biological subjects. It must be noted that the ENI petrochemical group is becoming increasingly involved in biotechnology and that it is partly government owned.

National Research Council (CNR): The CNR is responsible directly to the Office of the Prime Minister, and its mandate is to promote, coordinate and direct scientific research with a view to encouraging scientific and technical progress. It operates its own research institutes, supports research centers, funds laboratories in the universities and other institutes, is involved in technical training, and organizes collaboration with international scientific agencies. The president of the CNR directs it in collaboration with 11 national committees that are responsible for mathematical sciences; physical sciences; chemical sciences; biological and medical sciences, geological and mining sciences, agricultural sciences; engineering and architectural sciences; history, philosophy and philology; jurisprudence and political sciences; economics, sociology and statistical sciences; and technological research. These committees have a total membership of 140, with 116 representatives from universities and research institutes (2). This heavy representation of the faculties of universities has increasingly become a subject of controversy.

The total 1985 budget for the CNR was Lit. 827 billion ($432.9 million)*, of which Lit. 17 billion ($8.9 million) went to Biological and Medical Sciences. In the biological sciences, 62 percent went to government research institutes (many CNR), 4.7 percent to grants, 2.3 percent to contracts and 31 percent for conferences, publications and training (3).

In biology, there are 21 CNR institutes and 20 research centers with a total of 803 staff scientists (4). An important new development was the creation of Progetti Finalizzati (Finalized Projects) in 1976 that were directed towards economic problems of national importance. These projects are also aimed at stimulating cooperation between the government institutes and industry, as is indicated by the distribution of such funds in 1984 (2):

Administration	4.12 percent
CNR	9.85 percent
University contracts	32.35 percent
Industry and other organizations	53.68 percent

In 1982, the second generation of Finalized Projects was approved with a total budget of Lit. 590 billion ($309 million) for the period 1985-1988 (5). Of the fourteen projects, five were in the biomedical area and one in agriculture (see Table 1). The two that are most closely linked to biotechnology are genetic engineering and oncology.

*Average exchange rate for 1985: Italian lira (Lit.) 1,910 = $1.

.085

Table 1.
CURRENT & PLANNED FUNDING OF SECOND GENERATION FINALIZED PROJECTS IN BIOLOGICALLY RELATED SUBJECTS

Title of Project & Year Approved	Duration (in years)	Expenditure in millions Lira ($ equivalent*)							
		1985	1986	1987	1988	Total			
Preventive & Rehabilitative Medicine (1982)	5	13,174 ($6.9M)	13,000 ($6.8M)	6,375 ($3.3M)	--	32,549 ($17M)			
Control of Infectious Diseases (1982)	5	3,171 ($1.7M)	3,987 ($2.1M)	2,125 ($1.1M)	--	9,283 ($4.9M)			
Genetic Engineering (1982)	5	3,919 ($2.1M)	4,908 ($2.6M)	2,550 ($1.3M)	--	11,377 ($6M)			
Biomedical & Health Technology (1982)	5	2,962 ($1.6M)	2,860 ($1.5M)	1,275 ($670k)	--	7,097 ($3.7M)			
IPRA-Increase in Productivity in Agricultural Resources (1982)	5	26,359 ($13.8M)	33,176 ($17.4M)	17,786 ($9.3M)	--	77,321 ($40.5M)			
Oncology (1983)	5	20,412 ($10.7M)	24,000 ($12.6M)	24,000 ($12.6M)	24,000 ($12.6M)	92,412 ($48.4M)			
	Third Generation Finalized Projects (UNDER CONSIDERATION)								
		1986	1987	1988	1989	1990	1991	1992	Total
Biodiagnostics & Bioinstrumentation (1986)	5	4,500 ($2.4M)	10,000 ($5.2M)	11,000 ($5.8M)	12,000 ($6.3M)	4,500 ($2.4M)	--	--	42,000 ($22M)
Biotechnology (1986)	6	5,000 ($2.6M)	10,000 ($5.2M)	19,000 ($9.9M)	21,000 ($11M)	22,000 ($11.5M)	11,000 ($5.8M)	--	88,000 ($46.1M)

SOURCE: Annual Report, 1985, President of CNR.
*Average exchange rate for 1985: $1=Lit.1910.
M = millions

Planning is currently under way for the third generation of Finalized Projects (see Table 1). Of 10 projects approved thus far, one is in biotechnology involving a total of Lit. 15 billion ($7.85 million) for the period 1986-1991 (5). Minister Granelle also announced an allocation of Lit. 1,000 billion ($523.5 million) for a National Research Project in Biotechnology for the 1986-90 period. Aimed at launching Italy into the international biotechnology market, the project will be divided between the medical/pharmaceutical, chemical, and agricultural/food production sectors. Funding includes Lit. 100 billion ($52.3 million) for personnel formation and training, Lit. 400 billion ($209.4 million) for the financing of the National Research Program, Lit. 250 billion ($130.8 million) for public research organizations such as the National Research Council, and Lit. 250 billion ($130.8 million) for incentives to industry.

In 1984, the CNR tried to focus many of its research projects into strategic programs in order to maximize the use of its existing resources and to promote interdisciplinary collaboration. Of the strategic program classifications, two are in the biological area (Table 2) with Lit. 2.75 billion ($1.4 million) for advanced technology in biology and Lit. 2.5 billion ($1.3 million) for physics and chemistry of biological systems (5).

International Cooperation: Though in principle Italy's main international efforts should be in the framework of the EEC and Eureka programs, two of its most recent actions lie outside of it. UNIDO is establishing an International Center for Genetic Engineering and Biotechnology (ICGEB) with two separate research centers located in Trieste and New Delhi. Italy has announced that it will contribute Lit. 63 billion ($33 million) towards the establishment of the Trieste center with obvious hopes to profit from its R&D programs (6). Italy and the U.S. have also signed a cooperation agreement that will provide regular exchanges of information on research, production and registration of new pharmaceuticals and processes developed by biotechnology.

Ministry of Health: At the research level, this Ministry is responsible for Istituto Superiore di Sanita (ISS, Institute of Health) which not only carries out research (see section on Research Institutes), but also carries out important regulatory functions in toxicology, food safety, environmental problems, and rDNA issues. By determining the drugs and pricing of products that will be covered by national health insurance, the Ministry is also in a position to stimulate or inhibit the introduction of new biotechnology products.

National Commission of Biotechnology (Comitato Nazionale di Biotecnologia): In order to formulate a more coherent policy towards biotechnology, the Minister for Scientific Research, Mr. Luigi Granelli, created the National Committee for Biotechnology composed of 20 experts including representatives from companies such as Farmitalia, Sclavo, Sorin Biomedica, and Montedison. The commission is chaired by Mr. Granelli and has Professor A. Falaschi, director of the CNR Institute of Genetics, as co-chairman. The Commission has completed its deliberations, and made its recommendations to the government, but these have not yet been made public. Nevertheless, it is understood that the Commission has urged the government to take the following measures:

Table 2.
STRATEGIC PROGRAMS IN 1985

Program	Funding in millions Lira*	CNR	Number of Grants	% of Total Funding
Information Science	5,740 ($3M)	4,700 ($2.5M)	62	24%
Territory & Environment	5,220 ($2.7M)	4,200 ($2.2M)	59	22%
Advanced Technology in Biology	2,750 ($1.4M)	1,550 ($810k)	21	11.5%
Physics & Chemistry of Biological Systems	2,465 ($1.3M)	2,465 ($1.3M)	40	10%
Advanced Technologies	3,605 ($1.9M)	3,165 ($1.7M)	31	15%
Economy Services	4,200 ($2.2M)	2,900 ($1.5M)	63	17.5%
Total	23,980	18,980	276	100%

*Average exchange rate for 1985:$1=Lit.1910.
M = millions, k = thousands

(1) increase the support of basic research, both at government institutes and universities,

(2) target certain priority areas, specifically genetic engineering,

(3) to strengthen certain existing centers and convert them into centers of excellence, and

(4) promote applied research and establish national programs.

Elements of this proposal already exist in the present CNR system, but not in a coordinated manner. The creation and mandate to the Commission have been favorably received by both the scientific and industrial communities.

While in most other European countries attention has been focused on the government role in better coordination of R&D, and in particular, the creation of effective mechanisms for technology transfer, most individuals interviewed felt that Italy still lacked a scientific infrastructure, something that could only be provided by the government. The most severe criticism was leveled at the CNR, which was considered a bureaucratic organization whose policies are determined by national committees with a majority representation of university faculty members (generally considered to be conservative). In 1986, Science Minister Granelli submitted proposed legislation to the Interministerial Council which would deal with many of these problems, such as the lack of effective peer review, the scarcity of interdisciplinary collaboration as well as of close relationships between institutes and universities, and institutes and companies, the inadequate salary structure of CNR researchers, and the inflexibility of the personnel system. Parliament action is expected early next year.

The industrial sector has attributed the slow growth of biotechnology to the weak scientific base and to the lack of a political will to address this problem. Beyond the immediate issues of the scientific policy, the lack of a patent law until 1978 and the policies for pricing and payment by the Ministry of Health have discouraged Italian companies from investing in R&D.

III. UNIVERSITIES AND RESEARCH INSTITUTES

Three of the four principal biological research centers in Italy were visited. These were the CNR Institute of Genetics (Pavia), the CNR Institute of Cell Biology (Rome), and the Institute of Health (Rome). (The other is the Institute of Genetics and Biophysics in Naples.) The strongest university departments were said to be those at the universities of Milan, Rome and Naples, but arrangements could not be made to visit those. In general, it is felt that the most important research activities are carried out in the research centers rather than at the universities.

(a) Financial support: Funding for the institutes comes from three different sources: civil servant salaries come directly from the appropriate ministry or agency; an ordinary budget then covers the overhead costs; and grant support covers the majority of the research costs. For example, the

large Institute of Health spends some Lit. 14 billion ($7.3 million) on salaries, Lit. 30 billion ($15.7 million) on its ordinary budget, Lit. 1 billion ($523,000) from CNR grants, and Lit. 500 million ($262,000) from other grants (7). The level of funding is low and it has its most severe impact on research costs. The second series of Finalized Projects will help to alleviate the problem by providing some $4 million and, if the third series of projects is approved, an additional $5 million will be made available for 1986 (5).

In the visits to the institutes, the laboratories were well equipped, though the facilities were cramped and outmoded except for the Institute of Genetics which had just moved into a new building. While the funding was judged to be adequate, the whole procurement system was considered to be inefficient and costly. The other severe problem was the salary scale for scientists, which at the CNR started at Lit. 13.2 million ($6,900) per year and reached a maximum of Lit. 21.6 million ($11,300) per year (8). The situation was considerably better at the Institute of Health, where the salaries ranged from Lit. 25 million ($13,000) per year to Lit. 60 million ($31,400) per year (7).

(b) Scientific research: Some of the principal research groups in Italy were in classical biochemistry and pathology. The appearance of groups in genetics, molecular and cell biology originated with the creation of the International Laboratory of Biochemistry and Biophysics in Naples. Table 3 summarizes some of the major research themes at the institutes visited. During the past few years, there has been an increase in research in immunology and in plant biology (particularly in gene transfer in plants). Although individual laboratories are capable of good research, there is little evidence of a determined effort to set standards for scientific excellence, to promote interdisciplinary research, and to establish a network of researchers. It has been suggested that individual research projects can succeed as long as they do not depend on a well developed infrastructure and on close collaboration with other groups. It remains to be seen whether the advice of the Commission will lead to a consolidation of key groups at certain selected centers.

(c) Institute-Industry Interactions: There was little evidence of close cooperation between academic researchers and industry. In the case of the Institute of Health, this was deliberate in order to prevent a conflict of interest with the industries that were being regulated. Both the universities and the CNR can accept industrial contracts, but while the universities are fairly flexible in how the funds can be used, the CNR is prevented from using them for salaries. Most academic researchers seem reluctant to work on industrial projects.

(d) Staffing: The shortage of scientific positions generates a large number of applicants for any opening, but the number of qualified scientists is still limited. A significant pool of Italian scientists remains abroad, mainly in the U.S., in the absence of attractive opportunities at home. The permanent nature of CNR appointments and the small number of postdoctoral positions makes for a low rate of turnover with very few possibilities for young scientists.

Table 3.
INSTITUTES

	CNR Institute of Genetics (Pavia)	CNR Institute of Cell Biology (Rome)	Institute of Health (Rome)
Main Research Themes	1.Development of cloning vectors for E.coli & beta subtilis.	1.Mechanism of nerve growth factor.	1.Gene expression of malarial parasites.
	2.Development of virus vectors.	2.Genetics of HLA antigens.	2.Function of kinetoplast DNA in trypanosomes.
	3.Use of liposomes & vectors for gene transfer to plants.	3.Molecular biology of immunoglobulins.	3.DNA repair in mammalian cells.
	4.Cloning & expression of genes from human thymus.	4.Molecular biology of T-antigens.	4.Use of viral envelopes for gene transfer.
		5.Processing of tRNA.	5.Mechanisms of interferons & interleukins.

(e) Education: As in other European countries, there was a sharp increase in the number of university students in the 1970's, but the Italian university system did not undergo a major expansion, nor were there extensive curriculum changes. Training in biology takes 5-6 years, but there is little screening of the students and the courses are highly theoretical with limited exposure to laboratory techniques. There are no Ph.D. programs in some Italian universities, and the government supports Ph.D. students with scholarships worth about Lit. 10 billion ($5.23 million) per year. Elsewhere, the principal research institutes accept fifth and sixth year undergraduates, or graduates, and train them in-house. Frequently, these individuals continue their training by spending a period of postdoctoral research in the U.S. or elsewhere in Western Europe. Though admittedly ad hoc, this system provides a mechanism for selection and training of researchers in the biological sciences.

IV. INDUSTRY

At present, the industrial sector is in a much stronger position to develop biotechnology than either the government or the research organizations. The three major Italian industrial groups, ENI, Fiat and Montedison (ranked 3rd, 25th, and 56th in Fortune's International 500) (9) have increased their investment in the biotechnology related areas. Both ENI and Montedison are chemical groups that produce petrochemicals and their derivatives while Fiat is one of Europe's largest automobile manufacturers. Historically, their expansion coincided with a growing market for their products, but this involved a mature technology that was not dependent on extensive R&D. More specifically, the pharmaceutical companies took advantage of the lack of a patent law to manufacture drugs developed elsewhere. The end result has been that there is no long history of R&D in the pharmaceutical industry. The Gruppo Lepetit has established a solid reputation in pharmaceuticals and has now moved into the cloning and production of urokinase (otherwise known as plasminogen activator). It is now a subsidiary of Dow, the U.S. multinational. Sorin Biomedica is part of Fiat and specializes in medical devices. It is now developing diagnostic systems and one of its new products is a diagnostic kit for hepatitis B (the antigen was obtained from Biogen). Three pharmaceutical companies (two major ones and a medium-sized one) and an industrial research organization were visited.

ENIRICERCHE (ENI) is the partially government-owned chemical group which is undergoing a major restructuring of its activities away from petrochemicals and plastics into more specialized areas including pharmaceuticals. Its biotechnology activities are centered in a pharmaceutical company (Sclavo) and a research company (ENIRICERCHE). ENIRICERCHE was created as a separate company, bringing together two separate research centers located in San Donato Milanese (Milan) and Monterotondo (Rome). Its purpose is to provide central R&D for the ENI group. It has a staff of 600, including 370 scientists and 165 support personnel, about equally distributed between Milan and Rome (10). Twenty-one percent of its projects are in biotechnology, primarily at the Monterotondo center, except for the recombinant DNA work which is done in Milan (10). Funding depends partly on whether it involves long-term exploratory research (ENI support) or product/technology directed research (operating companies). Its primary research activities are:

- o Peptide synthesis: natural peptides with biological activity and their analogs.
- o Microbiology: strain characterization and genetics of industrially useful microorganisms.
- o Plant biology: physiology of fertilizer utilization by plants, genetic engineering.
- o Immobilized enzymes: applications to downstream processing.
- o Fermentation and downstream processing: computerization of control processes.
- o Biomass: ethanol production, waste treatment.

ENIRICERCHE is still in its shakedown phase, trying to define its relationship to operating companies as well as its priorities in long-term research. Though no detailed information on projects or corporate strategy is available, it appears that the most advanced project is the one in collaboration with Sclavo on active peptides. The other project areas seem much more diffuse and appear to be efforts to develop processes for some of ENI's other business areas such as agrochemicals and food processing.

FARMITALIA CARLO ERBA: Montedison is a major chemical group that owns 84.6 percent of Erbamont N.V. (11). All of Montedison's health care operations are now under Erbamont, and these include Farmitalia Carlo Erba (Italian), Lark (Italian), Adria Labs (U.S.), Kallestad Lab (U.S.), and Alpharm S.A. (Switzerland). Farmitalia Carlo Erba is the largest Italian pharmaceutical company with a long history in antibiotic production (much of it in collaboration with multinationals such as Cyanamid, Lederle and Merck). Its sales figures and principal products appear in Table 4. Farmitalia's sales represent about 2.7 percent of Montedison's global sales. Approximately 60-70 percent of the pharmaceutical sales are in foreign markets, with half of those in the U.S. (12). The best selling product is Adriamycin, a widely used anti-cancer agent.

Farmitalia has an R&D division with a staff of approximately 800, of which a third are scientists (12). It developed a capability in genetic engineering and like many others, cloned and expressed interferon but gave it up as a commercial project. As indicated in Table 4, its main efforts are in new rDNA blood products such as calcitonin and altered monoclonal antibodies for cancer therapy. They feel that in these new biotechnology projects, there is a severe shortage of qualified scientists and thus there is a need to collaborate with small U.S. biotechnology companies like Unigene (cloning and expression of calcitonin) and Cytogen (binding of Adriamycin and ricin to monoclonal antibodies).

The Montedison group is the second largest private industrial group in Italy (after Fiat). It is involved in a major restructuring moving away from chemicals and energy into pharmaceuticals, retail sales and financial services. At present, the Erbamont pharmaceutical group accounts for only 10 percent of sales. In order to finance its diversification Erbamont, which is traded on Wall Street, is trying to raise $200 million by the sale of additional stock (11). Farmitalia will also try to raise $259.5 million in the Milan stock market (13). These funds will be used for internal development within Erbamont, but there are also plans for acquisition of both

Table 4.
CHARACTERISTICS OF ITALIAN COMPANIES VISITED

	Farmitalia Carlo Erba (Montedison)	Recordati	Sclavo (ENI)
Annual sales for 1985 in millions of $	$527	$67.2	$125
Net Profit for 1985 in millions of $	$52.4	$4.8	n/a
Major products	Tetracyclines Cephalosporin Anti-cancer drugs (Adriamycin) Lysergic acid Aspartame	Anti-inflammatory drugs Anti-hypertensive agents Antibiotics Urinary tract anti-spasmodics OTC preparations Active ingredients & intermediates	Blood Products Vaccines Diagnostics Clinical instrumentation
R&D Expenditures in millions of $ (% of sales)	$47.4 (9%)	$7.1 (10.5%)	$11.25 (9%)
Areas of R&D	Cloning & production of calcitonin Binding of anti-cancer drugs to monoclonal antibodies Production of secondary metabolites by plant tissue culture New antibiotics	Human monoclonal anti-bodies for diagnostics Drug delivery systems	rDNA vaccines Beta & gamma interferons Interleukins
Agreements with U.S. Biotechnology Companies	Joint R&D with UNIGENE Joint R&D with Cytogen	Production & marketing with Syntex Joint R&D with Hana Biologics (5% equity) Joint R&D with Alza Joint R&D with FMC	Joint R&D with Chiron

products and companies. Consistent with this have been the recent attempts by Montedison to take over Fermenta, the Swedish pharmaceutical and biotechnology company at a cost estimated to be Swedish krona 3 billion ($427.96 million) (14). This is one of the largest foreign acquisitions by an Italian group. In line with this, the management of R&D at Farmitalia is being reorganized and its long-term strategies reexamined.

RECORDATI is considered one of the more aggressive mid-sized Italian pharmaceutical companies. It went public in 1984, at a time when a number of other Italian companies were being acquired by multinationals. It has annual sales of $67.2 million, of which some 40 percent is exported (15). Two-thirds of sales are pharmaceuticals, and one-third fine chemicals (mostly pharmaceutical intermediates) (15). As Table 4 illustrates, Recordati deals in a wide range of pharmaceutical products ranging from antibiotics to new over-the-counter (OTC) preparations. Many of the active ingredients are purchased and then formulated, packaged and sold by Recordati. Its new investments in biotechnology are in the area of human monoclonal antibodies and drug delivery systems. Human monoclonal antibodies are being used in diagnostic kits for hormones while the drug delivery systems will be used to administer anti-hypertensive and anti-convulsant medications.

Recordati has made effective use of a network of foreign partners, both for R&D and for production/marketing (see Table 4). In a rather unusual move for a firm of its size, it has a small international Scientific Advisory Board which not only helps set R&D policy, but assists in recruitment.

SCLAVO is the pharmaceutical company of the state owned ENICHEM, which is itself part of the ENI group. Sclavo has a traditional line of products based on blood products and vaccines, but unlike Farmitalia, only 15 percent is exported (16). The profits are estimated to fluctuate between 1-3 percent on sales of about $125 million (17), lower than for the other companies visited. Sclavo has recently built a new biotechnology center in Siena and seems to have made the most serious commitment to biotechnology. This center has a staff of 100 and is organized into five laboratories: biochemistry, molecular biology, cell biology, immunopharmacology and immunochemistry (18). It has capabilities in genetic engineering, monoclonal antibody production and use of yeast and human cell cultures for the synthesis of biological compounds. As indicated in Table 4, these technologies are being applied to a broad spectrum of new products ranging from diagnostics and vaccines to biological response modifiers. Sclavo has had the same difficulties in recruitment as other Italian companies and has made a deliberate effort to attract Italian scientists working abroad. It has an R&D agreement with Chiron for production of interferon in yeast and is actively seeking collaboration with U.S. universities.

Though Sclavo seems to be in a good position scientifically, its financial position is more problematic. Its market is primarily domestic and is centered around hospitals. Delays in payment by the government and difficulties in having products listed in the Prontuario (the official register of approved drugs) result in marginal profits. Therefore, there is little likelihood of further expansion at a time when their new project areas are facing intense competition from both major multinationals and aggressive new biotechnology firms.

INDUSTRIAL OVERVIEW

The characteristics of the three companies are summarized in Table 4. Most of the industrial activity in Italy seems directed towards pharmaceuticals and diagnostics. All three of the companies visited have well established product lines, but their profitability is associated in large measure with their export sales. None of them has a major presence in the U.S. Farmitalia and Recordati have made extensive use of external agreements (joint R&D, production, marketing) in order to avoid the expense and time consuming search for new products. Sclavo has attempted to develop its own in-house capabilities to a larger degree and move into new product areas. The same tendency is observed with ENIRICERCHE, except that there the effort is much more diffuse.

Neither the companies nor ENIRICERCHE show much interest in collaboration with universities or CNR institutes. The limited science base and the lack of venture capital make it extremely difficult to create new biotechnology companies. Therefore, in the near future, both basic research and industrial development in biotechnology will lie in the hands of the larger Italian companies.

V. CONCLUSION

It is fashionable to downplay the role of government in high technology and industrial development. Italy provides an object lesson on those activities that seem to be responsibilities of the state and for which there do not seem to be valid substitutes. The Italian government has followed a policy of benign neglect that has stunted the growth of a scientific and technical infrastructure. In biotechnology, this is reflected in:

- o the limited number of first-class research laboratories,
- o the lack of a modern biological curriculum and a shortage of scientists,
- o the absence of mechanisms for technology transfer, and
- o the lack of incentives for technological innovation.

In the absence of government initiatives, the industrial sector has had to face up to these shortcomings, and holds the government responsible for the inadequate science base. The government on the other hand finds fault with the timidity of the companies in pursuing industrial R&D.

Of the other European countries, Spain is the one that most closely resembles Italy. Both have developed strong manufacturing sectors, but agriculture and tourism continue to play important roles in their economies. Both also suffer from an inadequate scientific and technical infrastructure and an outmoded university system. With its Socialist government, Spain has made important changes in science policy, established a Mobilization Program in Biotechnology, and made effective use of its principal biological research institute to create a critical mass of researchers. To this, will be added a

new Center of Biotechnology that will also be responsible for technology transfer.

The Spanish government has promoted and funded new industrial projects of a technological nature. Spain lacks a strong industrial sector with both the resources and the access to major markets. This is the principal motivation for attracting foreign companies with new technologies. Italy has proposed a National Program in Biotechnology and appropriated new funds to expand the research effort. However, the effective use of such funds requires fundamental changes in the structure of the universities and the CNR. So, it is likely that in the short-term, the major developments in biotechnology will occur within the major Italian industrial groups.

A long-time observer of the Italian scene remarked to me that, except for the Fascist period, the history (and grandeur) of Italy has revolved around its city-states. This agrees with the view that both scientifically and commercially, Italian enterprises will perform successfully as long as they do not depend on a national infrastructure. As has been noted in the Industry section, most of the companies have strategies that combine in-house research, external agreements, acquisitions and marketing deals to protect themselves from the defects of the Italian system.

Finally, American investments in Italy have continued to grow (an increase of 9.6 percent in industrial companies, 22 percent in commercial ones) with these companies now employing 250,000 Italians and accounting for 6 percent of Italian exports (1). Given the limited prospects of pharmaceuticals in Italy, it is unlikely that U.S. companies with biotechnology activities will establish themselves in Italy. On the other hand, it should provide good opportunities as a market for new products, services, and also as a source of investment.

ACKNOWLEDGMENTS

Carmine G. D'Aloisio, Commercial Officer, American Consulate General, Milan

Piera Gattinoni, Commercial Specialist, American Consulate General, Milan

Graziella Lucarelli, Commercial Specialist, American Consulate General, Florence

August Maffry, Jr., Commercial Attache, American Embassy, Rome

Gerald J. Whitman, Counselor of Scientific & Technological Affairs, American Embassy, Rome

REFERENCES

1. Economic Trends in Italy & Their Implications for the U.S., American Embassy Rome, February 28, 1986.

2. Italy: A Science Profile, The British Council, Second Edition, 1986.

3. Report of the President of the CNR on the State of Scientific & Technological Research in Italy, 1985.

4. CNR President's Report 1985 & the National Research Council of Italy, Rome, June 1985.

5. President CNR Annual Report, 1985.

6. Rohe, Dieter, Italy to Coordinate, Subsidize Its Biotechnology Efforts, Chemische Industrie, October 1985.

7. D'Agnolo, Giuliano, Director, Laboratory of Cellular Biology, Istituto Superiore di Sanita, Rome, personal communication, April 14, 1986.

8. Tocchini-Valentini, Glauco, Director, Institute of Cellular Biology, National Research Council, Rome, personal communication, April 16, 1986.

9. Fortune, August 1985.

10. Eniricerche, 1985.

11. Financial Times, London, April 16, 1986.

12. Spalla, Celestino, Head of Industrial Microbiology, Farmitalia, personal communication, April 4, 1986.

13. European Chemical News, March 10, 1986.

14. Financial Times, July 8, 1986.

15. Recordati, 1984 Annual Report.

16. Scrip, July 31, 1985.

17. Butti, Adriano, Manager, R&D, Sclavo, Milan, personal communication, April 6, 1986.

18. Sclavo SpA, Siena-Milan-Modena, Italy, A Presentation.

APPENDIX

ORGANIZATIONS AND INDIVIDUALS VISITED

GOVERNMENT

National Committee of Biotechnologies: Professor Arturo Falaschi, Vice Chairman.

RESEARCH INSTITUTES

Institute of Health (Istituto Superiore de Sanita): Professor Giuliano D'Agnolo, Director of the Laboratory of Cellular Biology.

CNR Institute of Genetics, Pavia: Professor Arturo Falaschi, Director.

CNR Institute of Cellular Biology, Rome: Professor Glauco Tocchini-Valentini, Director.

INDUSTRY

Farmitalia Carlo Erba: Professor Celestino Spalla, Head of Industrial Microbiology.

Recordati: Dr. Yves Galante, Head, Section of Biochemistry and Immunology.

Sclavo: Professor Adriano Butti, Manager, Research & Development.

ENIRICERCHE: Professor Pierluigi Rebora, Vice President, Research & Development.

OTHERS

Chimica Oggi (periodical): Silvana Maini, Editorial Assistant.

SECTION D

BIOTECHNOLOGY IN THE NETHERLANDS

SUMMARY

The Netherlands has a solid research base in biotechnology, with a number of large companies that can make effective use of new technologies. Government policy, as regards biotechnology, is well conceived, provides increased funding for academic and industrial R&D and tries to bring basic research into synchrony with industrial needs.

The Dutch government feels that international cooperation should primarily be within the framework of the EEC, the most important aspect being the harmonization of policies towards pricing of agricultural raw materials, intellectual property, regulation of products from recombinant DNA techniques and of new biologicals, as well as uniform environmental standards. It is acknowledged that, in many respects, the EEC will follow the U.S. lead.

Biotechnology activities in the Netherlands are located in the large, multinational companies. They tend to be conservative, with a strong focus on established product lines. Given their strong financial positions, they would not hesitate to obtain new technologies through contracts, joint ventures, investment or acquisition.

The role of government policy in the development of biotechnology in the Netherlands is worthy of continuing analysis, and may prove a valuable model for U.S. States with similar plans for economic development of high technology industries.

I. INTRODUCTION

The Netherlands is a prosperous, industrial nation of 14 million people. Its economy is dependent on exports, and it is one of the few nations with which the U.S. maintains a healthy trade surplus. However, over the past 6 years its economy has remained stagnant, and its current unemployment stands at 12.9 percent. A center-right coalition government was elected in 1982 and has implemented an economic policy that has decreased public expenditures by across-the-board cuts, reduced the deficit and stimulated expansion of the private sector. National elections were held in May 1986, and the performance of the economy was one of the major political issues. The center-right government was returned to power.

Like many other industrialized countries, the Dutch government has focused on the transition of its industry from manufacturing to high technology, and hopes that this approach will result in a drop in the politically unacceptable high rate of unemployment.

GOVERNMENT POLICY

In 1979, the Dutch government announced a new policy of Innovation-Oriented Research Programs (IOP). Its objective was to change the priorities of government funded research and make it more relevant to the economic development of Dutch industry. The initial effort involved two ministries, those of Education and Science and of Economic Affairs. Though not specifically directed towards biotechnology, it has been the first industrial sector targeted.

In 1981, the Program Committee in Biotechnology (PCB) was constituted and made a detailed proposal for the IOP in Biotechnology (IOP-b). IOP-b is coordinated by the Program Bureau Biotechnology of the Central Institute for Industry Development (CIVI), an autonomous organization that acts as a consultant to the government. IOP-b is administered and funded through the Ministry of Economic Affairs, and is divided into four areas: manufacturing, health care, agriculture, and environment. Each one has its own Program Committee with officials from the appropriate ministries and representatives from the universities and industry. This structure is designed to stimulate basic research in key priority areas and to integrate the new technologies into new economic development programs.

Basic research in the Netherlands is primarily carried out in university laboratories and is funded through grants. Fundamental research is funded by the Netherlands Organization for Pure Scientific Research (Nederlandse Organisatie voor Zuiver Wetenschappelijk Onderzoek, ZWO, the equivalent of our NSF) while applied research is funded by the Foundation for Applied Research (STW). In addition, the government has the Netherlands Organization for Applied Research (TNO) which maintains a network of laboratories that conduct research for both the government and industry. The total annual funding for research in the biological sciences has been estimated to be f. 100 million ($30.12 million)*. The IOP-b has a budget of f. 70 million ($21.08 million) for the period 1983-88, in addition to the regular funding (1).

The IOP-b has selected research topics and funds three types of projects:

(1) basic research in selected areas such as biochemistry, enzymology, microbiology, cell biology, genetics, and molecular genetics. Share of IOP-b budget: 15 percent [f. 10 million ($3.01 million)] (2)

(2) applied research in host-vector systems, somatic cell hybridization, biochemical engineering, and downstream processing. Share of IOP-b budget: 35 percent [f. 25 million ($7.53 million)] (2)

(3) integrated applied projects involving collaboration between universities, research institutes, and industry. These projects have to be initiated by industry and the maximum funding from the government is 45 percent. Share of IOP-b budget: 50 percent [f. 35 million ($10.54 million)] (2)

*1985 average exchange rate: Dutch florin (f.) 3.3214 = $1.

In principle, the selection of proposals in basic and applied research is based on scientific quality. The IOP-b uses the same scientific review committees as the ZWO and STW. This not only assures the maintenance of scientific standards, and rational use of financial resources, but also promotes IOP-b policies in the research funding agencies.

Applied research is also carried out by the Netherlands Organization for Applied Research (TNO) which is a government agency composed of 35 institutes with 7 of them involved in biotechnology. The total TNO budget is some $60 million per year and the total staff numbers 5,000 (3). The TNO institutes receive grants from ZWO, and act as major centers for contract research both for other government organizations and for private industry. The three TNO divisions involved in biotechnology are:

TNO Food Analysis Institute (Zeist): production of food additives, extraction of raw materials and beverage technology.

TNO Division of Technology for Society (Zeist, Apeldoorn, Delft): production of fine chemicals, bioprocess techniques, waste treatment.

TNO Medical Biological Laboratory (Rijswijk): novel pharmaceuticals, monoclonal antibodies, vaccines, and DNA probe technology.

The IOP-b focuses on both basic and applied research carried out at non-profit institutions such as universities and research institutes. In addition, the Ministry of Economic Affairs has a number of other programs that support industrial R&D and promote new industrial activities. These include:

(a) In research: The Innovation Stimulation Regulation (INSTIR): this is a subsidy for wage costs related to R&D in the Netherlands. It involves up to 40 percent of wages ranging up to f. 300,000 ($90,323) in 6 months or 15 percent of wages ranging from f. 300,00-2.5 million ($90,323-$752,695). In the case of contract R&D, the extent of the subsidy is 80 percent (4).

Attention Policy for Biotechnology: this is an outright grant for research covering up to 50 percent of the costs and reaching a maximum of f. 3 million ($903,233) per project (5).

(b) In product development: Technological Development Credit: this is a credit to finance new products, new technologies and new services, and is intended for the development stage. This loan can cover up to 60 percent of the development cost with an interest of 5 percent. In the event of technical or commercial failure the loan is written off. The Industrial Development Fund has f. 250 million ($75.27 million) of which f. 50 million ($15.05 million) are for INSTIR and f. 200 million ($60.22 million) for Technological Development Credits (5). At the present there is support for 34 projects which are distributed in the following manner: 31 percent in food processing, 19 percent in pharmaceuticals, 19 percent in fine chemicals, 14 percent in plant biology, 10 percent in engineering, and 7 percent in equipment (5).

(c) in financing of new industrial activities: under the Investment Credit Act (WIR), technology transfer to a Dutch corporation is eligible for a 12.5 percent investment credit (6).

The Society for Industrial Projects (MIP): the MIP Equity Fund invests in new enterprises in the Netherlands. It is capitalized at f. 1,000 million ($301 million) of which f. 575 million ($173.12 million) has been invested. Funds come from the government (57 percent) and large institutional investors (43 percent) such as banks, pension funds and insurance companies. It takes a minority position amounting up to 49.9 percent with the level of participation being at least $1 million (7).

Private Participation Scheme (PPM): the government guarantees up to 50 percent of the losses of any given project in which officially recognized venture capital companies participate. The venture capital companies must limit their investment in any project to f. 4 million ($1.2 million) and invest at least 60 percent of initial capital within 4 years of establishment (8).

The overall government policies directed towards biotechnology are summarized in Figure 1. All of these have been used aggressively to promote joint ventures with foreign companies, especially American ones.

III. UNIVERSITIES AND RESEARCH INSTITUTES

There are seventeen institutions of higher education in the Netherlands, but rather than selecting one or two centers of excellence, the IOP-b has established multidisciplinary applied research projects at five universities with Wageningen focusing on agriculture, Utrecht in health care, Delft-Leiden in fermentation and downstream processing, and the two Amsterdam universities on bacterial and yeast physiology. The universities of Delft and Leiden have formed a joint biotechnology program as have the University of Amsterdam and the Free University of Amsterdam.

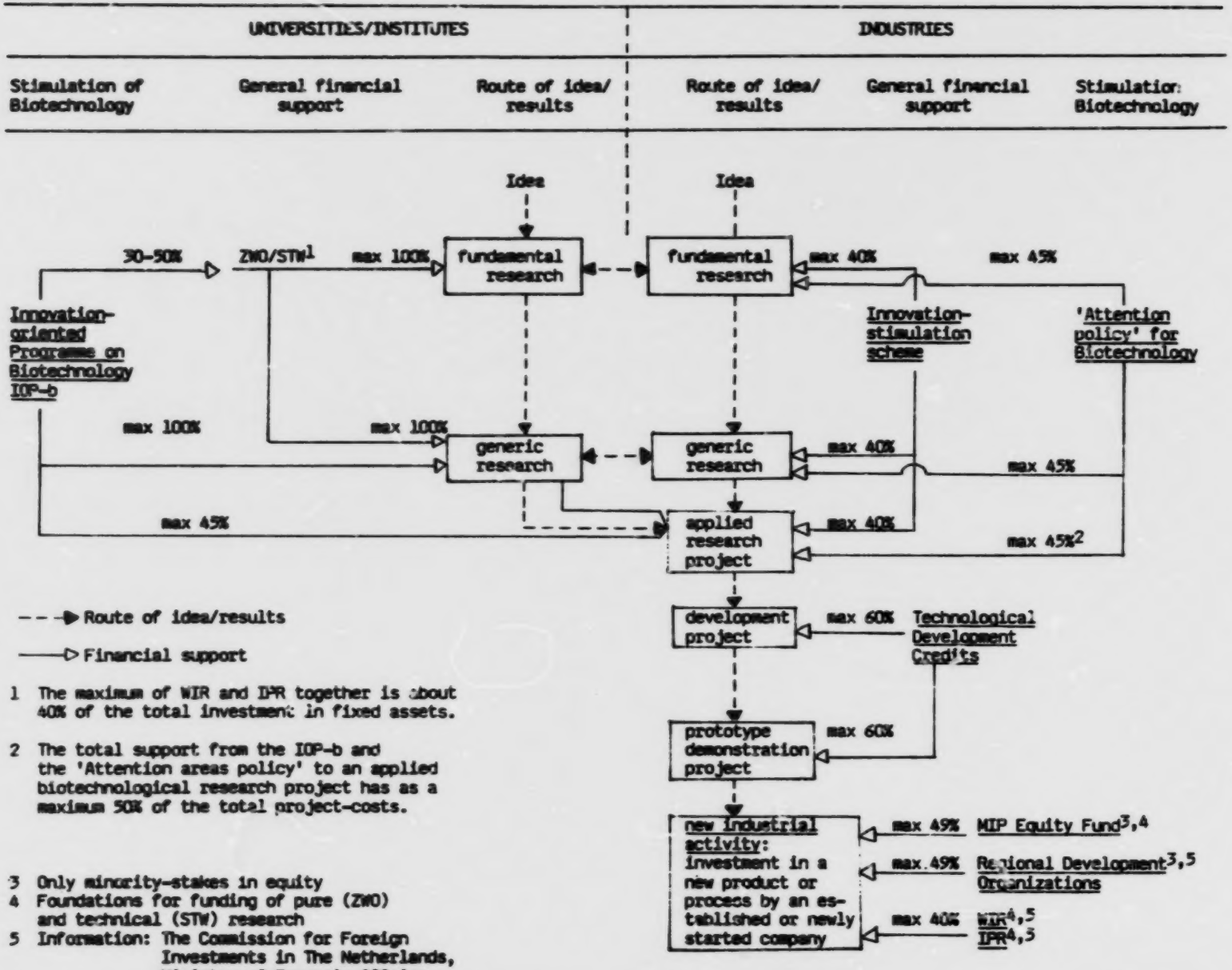
(a) Financial Support: In the universities visited, the IOP-b grants have been significant, though their effect is largest in the applied and integrated applied project categories. Spending to date on the four sectors covered by the IOP-b is (9):

Manufacturing	f. 10.5 million	$3.16 million
Agriculture	f. 4.4 million	$1.32 million
Environment	f. 12 million	$3.6 million
Health care	f. 400,000	$120,400

In the period from 1981-85, the number of researchers increased from 1,600 to 2,000 with the addition of 250 in basic research and 150 more in applied projects. Over the past year, TNO alone has increased the number of researchers by 41. Though the IOP-b budget represented only 7 percent of the total funding for research in the biological sciences, Leiden and Wageningen estimated that IOP-b funds would account for some 25 percent of their research budgets. In addition to this, IOP-b attracted individual contracts from government and industry. In the case of the enzymology research group at Leiden, industrial support was estimated at 25 percent. The program at the University of Amsterdam was unique in that it took advantage of a restructuring of the university which resulted in the elimination of the

Figure 1.

Governmental possibilities in The Netherlands for general and specific biotechnology-oriented financial support of the development of an idea till its application in the market



1 The maximum of WIR and IPR together is about 40% of the total investment in fixed assets.

2 The total support from the IOP-b and the 'Attention areas policy' to an applied biotechnological research project has as a maximum 50% of the total project-costs.

3 Only minority-stakes in equity
4 Foundations for funding of pure (ZWO) and technical (STW) research
5 Information: The Commission for Foreign Investments in The Netherlands, Ministry of Economic Affairs

BEST COPY AVAILABLE

Departments of Pharmacy and Geology. Some of the savings were used for the establishment of a Biotechnology Program (f. 2.5 million ($752,700)/yr.) (10). This program is run in collaboration with the Free University of Amsterdam whose share of the program is funded by the IOP-b.

This net increase in research funding has taken place against a general background of budgetary cuts at the universities. The IOP-b funds cannot be used for capital equipment or laboratory construction which are deemed to be the responsibility of the universities. Such limitations in infrastructure may slow down the effective use of new research funds. University researchers whose projects do not fall into priority areas are at a serious disadvantage. As university laboratories move into more "relevant research" to obtain IOP-b grants and external contracts, they come into open competition with TNO institutes. One attempted solution is to develop multilateral projects involving universities, TNO and industry, but such schemes have scientific and administrative problems that are not easily resolved.

(b) Scientific Research: The Netherlands has had a solid research base in the biological sciences, particularly in some of the more classical areas such as enzymology, energetics, ribosome structure and function, bacterial and yeast physiology. Given the important role of the pharmaceutical and agricultural/food processing industries, R&D in plant breeding, fermentation and downstream processing have been particularly well developed. Dutch scientists have been slower in developing the new technologies of molecular genetics for studies of animal and plant cells, and applying them to industrial processes. This was due in part to the ban on recombinant DNA research during the 1970's, and, in part, to what is seen as a fragmentation of the research effort and a hesitancy to compete in a very rapidly moving research field.

In order to preserve academic freedom, the multidisciplinary applied research projects have been constructed around the best existing groups. A program manager and a steering committee are responsible for each program, but they act as coordinators with no authority to allocate funds or personnel. The IOP-b programs at three universities and one TNO institute were examined (Table 1). There is apparent duplication in certain areas, e.g., plant biotechnology, industrial fermentation and downstream processing. Though the programs are too new to be scientifically evaluated, they have produced certain beneficial changes: set standards for scientific excellence, increased scientific collaboration and communication, and promoted better use of resources. As one researcher put it, "We are all talking to each other." It is not unusual for a program to involve groups in three or four departments in two different universities which do not necessarily share space or equipment. When the program is well conceived in terms of a communality of interests, there has been satisfaction with the results. Alternatively (e.g. in Leiden), dissension between groups has led to the probable reorganization of one of the programs. Though not necessarily related, it was pointed out that a number of senior faculty members had left in order to join the staff of a major company, Gist-Brocades. In the case of universities and TNO institutes, it is felt that the best arrangement is one in which the university groups carry out the basic research and the TNO develops industrial applications (e.g. projects for the construction of vectors for use in Aspergillus, development of a vaccine for hoof and mouth disease.)

Table 1.
CENTERS VISITED

	Delft-Leiden	Wageningen	Univ. of Amsterdam/ Free U. of Amsterdam	TNO Medical Biological Institute
Research Theme	Fermentation and Downstream Processing	Agriculture	Bacterial & Yeast Physiology Fermentation	Medical
Multidisciplinary Projects	1.Incomplete Microbial Oxidations	1.Food & Feed	1.Optimization of product formation by microorganisms (bacteria & yeasts)	1.rDNA techniques for production of pharmaceuticals
	2.Physiology & Genetics of Yeasts	2.Biocatalysts	2.Plant biotechnology	2.Molecular diagnostics
	3.Plant Cell Biotechnology	3.Waste Treatment	3.Production of Monoclonal Antibodies	3.Biocatalysts
	4.Bioreactor Design & Downstream Processing	4. Plant Genetics & Animal Health Care	4.Enzymology	4.Fermentation Technology
	5.Control			5.Downstream Processing
	6.Waste Streams			

(c) University-Industry Interactions: The university researchers visited felt that they had become more familiar with industrial requirements and that the IOP-b program has enabled them to attract more industrial contracts. This has also been facilitated by the creation of Transfer Offices at the universities. The Transfer Office at Leiden has three functions: (1) arrange contracts, (2) identify research findings of commercial significance, and (3) assist companies with technical problems by referring them to the appropriate university laboratory and encouraging them to locate in the bio-science park. In addition to the IOP-b programs, individual contracts were of two types: contact and direct. Contact ones involve industrial sponsors that provide some financial support (typically salaries for graduate students), and acquire access to research information. The university overhead in such cases would be negotiated at 10-20 percent. Direct contracts involve funding of a project with specific goals, with the university charging 100 percent overhead and retaining property rights.

As elsewhere in Europe, there is a fascination with the role of small, new start-up companies in the development of new technologies. Two efforts at establishing new biotechnology companies were described at Leiden. In the first one, a university laboratory doing research on restriction enzymes set up a small, commercial entity to sell the enzymes in the Netherlands (the major commercial suppliers were two American companies, and a German one). This involved use of university space and the hiring of additional technicians for production. Production served to meet the needs of the Dutch research community and the income covered the costs and probably subsidized the operation of the laboratory in question. However, the sales volume and income were insufficient for it to become a normal, commercial enterprise. This operation will cease and be taken over by Promega, an American biotechnology company moving into the Leiden science park. The second attempt at commercialization is Holland Biotechnology, Co., which functions in a manner similar to the Transfer Office. It tries to obtain contracts for university laboratories and sell some of their products (e.g., monoclonal antibodies). Leiden is actively promoting a science park specifically in biotechnology. It has succeeded in attracting three American companies: Promega (restriction enzymes), Molecular Genetics (agricultural molecular biology) and Centocor (monoclonal antibodies for cancer diagnosis and therapy).

R&D contracts are, potentially, an important source of funds for universities though there is some controversy as to whether they are a legitimate function for universities, and not best done in specialized institutions such as the TNO. The market for such services is limited by the small number of large companies in the Netherlands, which are quite capable of arranging their own contracts either in the Netherlands or abroad (see section on companies). The other possibilities are with the small or medium-sized companies, but these are often conservative and have low levels of R&D expenditures. If a small company has negligible in-house R&D, it is unlikely to make effective use of purchased research from external sources. This is not to say that government funding and increasing awareness does not improve the process of technology transfer from the more established university groups. For example, the Incomplete Oxidations group at Delft-Leiden has interested industrial partners for applications of its research. These involve two different types of companies:

(1) High tech, large company: enzymatic hydroxylation to manufacture intermediates in the synthesis of pharmaceuticals.

(2) Low tech, traditional company: role of oxidation in spoilage of cocoa to ensure better quality control in cocoa production.

Though there is extensive academic interest in the creation of new biotechnology companies, there is no evidence that spinoff from university research is significant.

(d) Staffing: the expansion of the universities in the 1970's has led to the existence of large staffs. The IOP-b program would provide an opportunity for some of the faculty to shift their activities into more applied projects. Most research areas are well represented except in fermentation and downstream processing, where industrial demand is very high. Appointments at the TNO and the Netherlands Cancer Institute are attractive, since they provide the opportunity to do full-time research and have excellent support and facilities.

(e) Education: at the present time the educational system in the biological sciences is similar to that in the U.S. with 4 years for an undergraduate degree and an additional 4 years for a Ph.D. The major difference with the U.S. is that unless they go abroad, many Dutch Ph.D.'s do not do postdoctoral work, but seek a permanent position either in university or industry. There has also not been curriculum development for advanced training beyond the Ph.D. or for retraining.

At all universities visited, there are plans to introduce a new educational program in biotechnology. This would consist of a 5-1/2 year program divided into two phases. In the first 4-year phase, the student would major in a regular subject (e.g., chemistry, biology). During the second 1-1/2 year phase, the student would take short advanced courses, do a feasibility study, and carry out a 1-year multidisciplinary project. The cost of such a new curriculum would be f. 2 million ($602,200) per year for a group of 20 students (10). Both faculty members and corporate managers mentioned serious industry opposition to the program on the grounds that it is both costly and unnecessary. A government move that may have serious consequences is the reduction of graduate student stipends from f. 3,000 ($903) per month to f. 1,400 ($421) per month (11). This has not resulted in a decrease in graduate student enrollment, but may have had some effect in the quality of students.

(f) Netherlands Cancer Institute: this institute is somewhat different from the others, in that it focuses on cancer research. It has an annual budget of f. 20 million ($6.02 million) from the Ministry of Health, and receives an additional f. 10 million ($3.01 million) for special projects, a significant proportion of this coming from the private Wilhelmina Foundation. It has a staff of 100, of which 50 are on the permanent staff (12). The Institute is minimally involved with industry, but perceives its function to be the pursuit of broad-based biological research and its application to the development of novel forms of cancer therapy.

IV. INDUSTRY

The biotechnology industry in the Netherlands is concentrated in a number of large companies. Four large companies were visited; two of them apply biotechnology to traditional food, beverage and consumer product lines, and the other two are involved in chemicals and pharmaceuticals. All four are multinationals, successful in their markets, and highly profitable.

HEINEKEN is one of the world's largest breweries with worldwide operations. It has annual sales for 1985 of f. 6,402 million ($1,027.5 million) with profits of f. 265.4 million ($79.9 million) (13). Its main products (in order of importance) are: beer, soft drinks, and wine and spirits. Of these, soft drinks represents the fastest growing market.

Most of Heineken's earnings are generated outside the Netherlands either by export of Heineken beer or production of other brands specifically formulated for individual national markets. The research department is small (50 staff), and its primary function is to support this business strategy by maintaining quality control and generating new beers. The more exploratory research focuses on three topics: (a) development of new barley strains, (b) characterization and development of new yeast strains; and (c) analysis and improvement of protein content in barley and malt. Not all of this research is carried out in-house, with a number of research projects being contracted out to groups in the Netherlands and abroad.

The view at Heineken is that the new biotechnology techniques will not make a major impact on its traditional business. They are aware that their strengths in yeast physiology and its application to fermentation processes can be exploited in new market areas. Two obvious candidates are the use of new recombinant yeast strains for the production of pharmaceuticals, and production and application of industrial enzymes. Present policy is to maintain a watching brief and follow technical and commercial developments in these fields.

UNILEVER is a huge Anglo-Dutch multinational with estimated annual sales for 1985 of f. 66,771 million ($20,103 million), mostly abroad. Net profits were f. 1,330 million ($400.4 million) (14). Its production is divided into 70 percent for the consumer market, and 30 percent for the industrial one, with three main product areas: food, cleaners and chemicals (15). Its major production facilities are in the Netherlands, U.K., U.S., and India.

The business strategy of Unilever is to consolidate into its traditional product areas and divest itself of companies that are unrelated to these. It was openly stated that Unilever does not know whether and/or how biotechnology will affect its future activities, but it is committed to the principle of corporate research. Its annual research budget is f. 1,1012 million ($304.7 million) with approximately 3 to 4 percent of that in biotechnology. Its central research division has five laboratories, one in the Netherlands (staff: 1,200) (15), two in the U.K. (with staffs of 1,200 and 250), one in the U.S. (staff: 1,100), and one in India (staff: 250). This last one will be expanded to better serve that whole region.

Unilever's product-oriented interests in biotechnology are in production of monoclonal antibodies for diagnostic uses, and development of oral vaccines for animals. The exploratory areas are:

- o fermentation: industrial production of enzymes through the use of recombinant DNA techniques and improved protein purification,
- o enzymes: development of immobilized enzyme systems for application in bioreactors, and
- o plant biology: use of genetic engineering for development of new plant strains for improved oil production (some early success with palm oil plants).

At the present time, there are no contracts with U.S. biotechnology companies and no significant contracts with Dutch universities. Unilever has been a strong advocate for government support of research in protein engineering (which is directly relevant to its interests in enzyme technology). Though there is an understandable reticence to discuss specific projects, information from other sources indicate that Unilever has made excellent progress in two project areas. One is the large-scale use of enzymes in non-aqueous solvents for esterification of fatty acids on a large-scale. Development of this type of technology is important for the use of enzymes in the production of chemicals. It is also collaborating with several universities on the relationship between structure and function of thaumatin, a natural sweet protein. Findings in this area would lead to development of a whole new class of food additives, both natural ones and those engineered by recombinant DNA techniques. Though actively pursuing its own research interests, Unilever will track developments in biotechnology but for the present will refrain from becoming seriously involved in new enterprises.

GIST-BROCADES is an older company that had started in the production of yeast for the baking goods industry and had then aggressively moved into antibiotics production and industrial enzymes. Its annual sales for 1985 were f. 1,851 million ($557.3 million) with net profits of f. 100.2 million ($30.2 million). Approximately 66 percent of their sales are abroad (16).

Gist-Brocades has four operating divisions: yeast and bread improvers, industrial products, pharmaceuticals, and other products. Sales in the first three divisions were roughly equal (almost a third each), but industrial products is the most profitable of the four. The company has a strategy of concentrating on the established product lines and all expansion and development of new technologies is consistent with that policy. It has a central R&D department with a staff of 600 which concentrates on microbiology and process engineering. The emphasis is to do all commercially relevant research in-house. It was difficult to obtain specific information on current R&D projects, but part of it involves improving their current product lines, e.g.:

- o increasing the productivity of the molds used for production of B-lactam antibiotics,

- o increasing yields and improving properties of industrial enzymes such as amylase and various proteases, and

- o production of blood factor VIII (used for treatment of hemophiliacs) in yeasts. This might indicate a shift towards production of naturally occurring biologicals for use in therapy.

This last project, as well as a number of studies to develop new strains of yeasts by genetic manipulation, are being done in a joint venture with Chiron, an American biotechnology company.

One R&D project area that has already had important commercial implications is that of waste treatment. Increasingly stringent Dutch regulations on the environment had encouraged studies into the use of anaerobic microorganisms for the digestion of biological wastes. A two-step waste treatment plant using bacteria immobilized on sand was designed and constructed to treat the biological effluents from their own industrial complex at Delft. In the first step, the waste is converted into acetic acid, and in the second step the acetic acid is converted to methane, which is then used to produce energy with which to run the plant. Two more waste treatment plants have been built for Gist-Brocades facilities in France and West Germany. The results are so promising, and the potential market sufficiently large, that there are plans for creating a fifth operational division for environmental control. In line with this, it has acquired the Biothane group, which has also developed technology in anaerobic effluent treatment. This would represent a major departure from the stated corporate policy.

AKZO is a company resulting from the merger of two large Dutch conglomerates in 1970. Its sales in 1985 amounted to f. 18.01 billion ($5.42 billion) with net profits of f. 843 million ($253.8 million). AKZO has seven operating divisions: ENKA, AKZO Zout Chemie, AKZO Chemie, AKZO Coatings, AKZO Pharma, AKZO Consumer Products, and AKZO America. Biotechnology activities are located in AKZO Pharma, whose sales account for 11 percent of the total, but contribute around 22 percent of the profits (17). The AKZO Pharma Division comprises five separate companies:

Organon International: ethical drugs
Diosynth: raw materials for pharmaceutical production
Organon Teknika: hospital supplies and hospital equipment
Chefaro International: non-prescription pharmaceuticals and diagnostics
Intervet International: veterinary medicines and vaccines

Though synthetic fibers and commodity chemicals are a major part of AKZO's business, they are subject to fierce competition and declining sales. It has, therefore, become AKZO's policy to move out of these product lines and concentrate on high-value added products such as coatings, specialty chemicals and pharmaceuticals.

Given the corporate policy, AKZO Pharma is a primary candidate for expansion. In sharp contrast to the other firms visited, it intends to exploit the new biotechnology, both in diagnostics and therapy. There is no central R&D department, such activities being an intrinsic part of each

operating company. The concept is that R&D must be product-related. A discussion of the impact of biotechnology on the different divisions of AKZO lead to the following statements: profit margins for production of specialty chemicals or veterinary medicines were very narrow, and agricultural products were too susceptible to government policies. Therefore, they would not be very attractive for R&D. Their major research theme is to acquire an understanding of how the human immunological system works. Its most near-term project is to develop a vaccine against pregnancy so as to further expand their present line of oral contraceptives. Its highest risk area is into the potentially lucrative market of cancer diagnostics and therapeutics.

During the past year, AKZO has moved to divest itself of its American synthetics firm ENKA, and create an acquisitions fund. It has acquired the diagnostics division of Warner-Lambert for a sum estimated at f. 400-500 million ($120.4-$150.5 million), and 50 percent of the operations of Litton Bionetics for f. 150 million ($45.16 million) (18). The Warner-Lambert operation would provide Organon Teknika with a mechanism to produce and sell diagnostic kits for AIDS, hepatitis, rubella, and pregnancy in the U.S. Part of the Litton operation was involved, also, in the production of diagnostic kits for both human and veterinary use. However, the key elements in the deal were a research institute and a management contract of a National Cancer Institute center in Frederick, MD. Research at the Litton Institute had progressed rapidly in the production of monoclonal antibodies against colon cancer. Use of these antibodies is currently in clinical trials. If successful, there are plans to set up a number of clinical treatment centers in Europe. The NCI contract would provide AKZO with a window on some of the most current research on oncogenes and their role in tumorgenesis. However, it is not clear at this time whether a foreign corporation can manage this particular contract with its possibility of technology transfer to a foreign country.

AKZO still counts on an acquisition fund of f. 1 billion ($301 million) and intends to continue its expansion into the U.S. Biotechnology is one of its key targets (19). Furthermore, it seems to be willing to explore the potential of totally new products created by biotechnology.

INDUSTRIAL OVERVIEW

The characteristics of the four companies visited are summarized on Table 2. All of the corporate managers were favorable towards the IOP-b, all of them had participated on the deliberations of the Program Committee, and many of them still were active in it. On the other hand, they were noticeably less enthusiastic than the academics.

The IOP-b has changed attitudes at the universities and made them more supportive of collaboration with industry. Communication has improved and industry is more aware of the research taking place. Almost unanimously, they felt that it was an error for universities to get involved in doing applied research; university departments should pursue basic research and train students. Additional funding should be used to make academic salaries more

BLANK PAGE

Table 2.
CHARACTERISTICS OF SELECTED DUTCH COMPANIES

	Heineken[1]	Unilever[2]	Gist-Brocades[3]	AKZO Pharma[4]
Annual Sales for 1985 in millions of $ (% incr from 1984)	1,927.5 (0.9)	20,103 (3.38)	557.3 (2.44)	5,420 (5.24)
Net Profit for 1985 in millions of $ (% incr from 1984)	79.90 (12)	400.4 (1.2)	30.2 (22.8)	253.8 (8.46)
Products	Beer Soft Drinks Spirits & Wine Others	Food Cleaners Chemicals	Yeast & Bread Improvers Industrial Products Pharmaceuticals & Animal Health Others	Man-made Fibers Salt Heavy & Specialty Chemicals Coatings Pharmaceuticals Consumer Products Other Industrial Products
R&D Expenditures in millions of $ (% of sales)	N/A	304.7 (1.52)	27.1 (4.86)	218 (13.4)
Areas of R&D	Protein composition of barley & yeast Yeasts	Edible oil products Immunology Microbiology	Molecular biology of yeasts Anaerobic effluent treatment	Monoclonal antibodies in development of diagnostic kits Vaccine against pregnancy rDNA for production of vaccines for use in animal health care rDNA for production of pharmaceuticals
Interaction with U.S. Biotechnology Companies	None	None	Joint venture w/Chiron Joint venture w/Shell	Acquisition of Warner-Lambert diagnostics division Acquisition of part of Litton Bionetics

1. Heineken Annual Report, 1985.
2. Unilever Annual Report, 1985.
3. Gist-Brocades Annual Report, 1985.
4. AKZO Pharma Annual Report, 1985.

comparable to those in the industrial sector, increase graduate student stipends, and modernize university facilities.

In principle, the companies were conservative in their R&D strategies, limiting those to product-related areas, and de-emphasizing exploratory research. All of the research would also be carried out in-house. Corporate decisions were also sharply influenced by government policies (e.g. pricing policies for agricultural raw materials, regulatory codes). With the exception of AKZO, the companies were uncertain as to how new biotechnology techniques would affect them, but all had introduced new techniques into their laboratories and were alert to any new developments in the U.S. and Japan. Being cash-rich, they would have no hesitation in purchasing the technologies and/or the companies if necessary.

The companies felt that if an R&D project was important to them, they were well placed to finance it, and the contribution from government programs was not significant. Gist-Brocades (the smallest one) stated that one of their projects (waste treatment?) might not have been pursued except for the government contribution. All were very positive about getting the government to back multidisciplinary applied projects in key areas (one mentioned frequently is protein engineering).

They all believe that in the Netherlands, the important activities will be in the big companies. At no point, did anyone mention any of the six, or more, small start-up companies in the Netherlands. There is curiosity about the three American biotechnology companies that are to begin operations at the Leiden Science Park. They have a healthy respect for the science and the entrepreneurial spirit of the small U.S. companies. The relatively high cost of research and the restrictive nature of Dutch labor laws are deterrents to the setting up of R&D projects of an exploratory nature. R&D contracts to U.S. biotechnology firms are an attractive and straightforward alternative pursued by at least two of the Dutch companies.

The IOP-b is perceived as another favorable initiative by the present government to improve the climate for business in the Netherlands. One important effect is that it has completely eliminated any opposition to projects using recombinant DNA techniques. Given the fierce controversy that raged during the 1970's, this is no mean achievement.

V. CONCLUSION

What is the current status of biotechnology in the Netherlands? It has a good, solid research base though not necessarily an outstanding one, and counts with a number of large successful companies that can make effective use of new technologies developed both there and abroad. In order to implement a shift from a manufacturing economy to a more high technology oriented one, both the government and industry have selected biotechnology as a target for future development.

The Dutch government has designed, and put into place, a program for biotechnology and is also making use of general policies for industrial

innovation to further stimulate this industry. Taken as a whole, the government policy is well conceived, provides increased funding for both academic and industrial R&D, and by identifying priority areas tries to bring basic research into synchrony with industrial needs. The most unusual aspect of this policy is that it is comprehensive, covering the whole spectrum from basic research to establishment of new companies. The active participation of scientists and industrialists, the commitment to scientific excellence, and the coordination by a non-government agency, CIVI, provide the basis for flexibility in decision making. Overall, it has created an atmosphere of excitement and cooperation between universities and industry.

It is too early to assess the results of such a policy, but it is likely that its most immediate results will be an improvement on the quality of research at the universities and institutes primarily by increasing multidisciplinary projects. There is an inherent danger (as pointed out by most industrialists) that the university scientists will become fixated with projects of "commercial significance" and industrial contracts, abandoning more fundamental work. Here as elsewhere, basic research is carried out at universities, and the authorities have chosen to ignore the fact that the health of the research enterprise is not independent of what happens to the universities. Issues of infrastructure (e.g. buildings and capital equipment), academic salaries, and graduate student stipends will seriously affect how effectively research funding will be used.

The government feels that international cooperation should be primarily within the framework of the EEC. The most immediate effect would be the creation of certain common services such as strain collections and data banks. Some of the university scientists also felt that it might be a source of research funds. The general consensus is that the most important function of international cooperation would be the harmonization of policies within the EEC towards pricing of agricultural raw materials, intellectual property, regulation of the products from recombinant DNA techniques and of new biologicals, as well as uniform environmental standards. It is also acknowledged that in many respects the EEC will follow the U.S. lead in such matters.

Biotechnology activities in the Netherlands are located in large companies. These are multinational, market leaders in their respective industries, and are good developers and users of new technologies. In their business philosophy, they tend to be conservative with a strong focus on their established product lines, and concentrate their research along those lines. The exception to this is AKZO which is under strong pressure in its established businesses, and is trying to move aggressively into new fields and gain access to the U.S. market at the same time. In doing so it has both identified the high-risk area of cancer diagnostics and therapy as a new sector, and made two large acquisitions in the U.S. including an R&D institute involved in cancer therapy. Though their preference is for internal research, they have a healthy respect for U.S. research capabilities. Given their strong financial positions, they would not hesitate to obtain new technologies from U.S. companies (particularly the smaller biotechnology ones) by contracts, joint ventures, investment or straight acquisition. This appears to be a general trend that had already been noted in an earlier report on

Finland and Norway. All of the companies also mentioned that they were deluged by proposals from U.S. biotechnology companies to the degree that one of the managers said, "If I read all of those proposals, I would have no time to do anything else." If the sale of U.S. technology were perceived to be in the U.S. national interest, then a better effort should be made to coordinate the marketing of technical services (i.e. focus the proposals to the product-oriented R&D of the companies).

Though one of the goals of government policy is the creation of new biotechnology companies, there was no evidence of new, significant industrial activities. When the issue was brought up, mention was also made of the three U.S. companies that were establishing themselves in the Leiden Science Park. Effective use had been made of the incentives for industrial innovation which provide government grants and credits for technology transfer from other countries into the Netherlands. Aside from creating new jobs, it is hoped that these moves will energize the small business sector. It should be noted that the WIR program which has been used to capitalize the building of new plants will expire in 1986, under sharp criticism for providing tax shelter to companies that had no significant sales, and for being primarily exploited by foreign companies.

In conclusion, the role of government policy in the development of biotechnology in the Netherlands is worthy of continuing analysis, and may prove to be a valuable model for U.S. States with similar plans for economic development of high technology industries. The rapidly changing situation in the Netherlands provides an interesting market for contract R&D and a distinct possibility for U.S. biotechnology companies interested in launching new operations in Western Europe.

ACKNOWLEDGMENTS

Mark Armitage, Commercial Specialist, Foreign Commercial Service, American Embassy, The Hague

Stan Harris, Commercial Counselor, Foreign Commercial Service, American Embassy, The Hague

REFERENCES

1. Schilperoort, R.A. & van der Meer, R.R., "National Biotechnology Development Programmes & Strategies (The Innovation-Oriented Programme on Biotechnology in the Netherlands)," January 1985.

2. The Netherlands Investment News, March 1985.

3. Stevens, Dr. W.F., Chairman & Director of the Medical Biological Laboratory, TNO, Rijswijk, the Netherlands, personal communication, October 23, 1985.

4. Ministry of Economic Affairs, Commission for Foreign Investment in the Netherlands, "Biotechnology in the Netherlands, A Strong Foundation -- A Shining Future."

5. Roos, Dr. H.R. & van den Bosch, M.C.F., Ministry of Economic Affairs, the Netherlands, personal communication, October 25, 1985.

6. Peart, Peter B., U.S. Audit Consulting Partner, Coopers & Lybrand, Amsterdam, the Netherlands, personal communication, October 25, 1985.

7. MIP Equity Funds: A Source of Capital in Europe.

8. The Financial Times, London, December 3, 1985.

9. Schilperoort, Dr. R.A., "Strategies for the Planning and implementation of the innovation-oriented programme on biotechnology," The Netherlands, busy in biotechnology, Proceedings of a symposium, May 29, 1985, Delft, the Netherlands, p. 12.

10. Neijssel, Dr. O.M., Microbiology Laboratory, University of Amsterdam, the Netherlands, personal communication, October 25, 1985.

11. Kossen, M.W.F., Gist-Brocades, the Netherlands, personal communication, October 22, 1985.

12. de Haas, M.G.O.M. & Roos, H.R., The Netherlands Cancer Institute, personal communication, October 25, 1985.

13. Heineken, Annual Report, 1984.

14. Unilever, Annual Report, 1984.

15. Keuning, R., Director, Unilever Research Laboratory, Vlaardingen, the Netherlands, personal communication, October 22, 1985.

16. Gist-Brocades, Annual Report, 1984.

17. AKZO, Annual Report, 1984.

18. The Financial Times, London, July 18, 1985.

19. The Financial Times, London, October 11, 1985.

APPENDIX

Individuals and Organizations Visited

Government

Program Bureau Biotechnology, Central Institute for Industrial Development (CIVI): Dr. R.R. van der Meer, Coordinator.

Ministry for Economic Affairs: Dr. M.C.F. van den Bosch, Development Research; Dr. H.R. Roos, Action Programs.

Program Committee on Health Care: Dr. N.A.J. Mul, Chief Officer of the Health Care Council on Biotechnology.

Program Committee on Environment: Dr. K. Visscher, Coordinator of the Environmental Program.

Program Committee on Agriculture

Universities and Research Institutes

Delft Technical University: Professor J.A. Duine, Head of Enzymology Group, Department of Biochemical Engineering.

Agricultural University at Wageningen: Professor Hendrik A. Behagel, Director of the Biotechnology Program & member of the Program Committee on Agriculture; Dr. Hans J. Dekker, Program Administrator.

University of Leiden: Dr. Adrian de Waard, Professor; Dr. H. van der Starre, Director of the Transfer Office.

University of Amsterdam: Dr. O.M. Neijssel, Microbiology Laboratory

Medical Biological Laboratory of TNO: Dr. W.F. Stevens, Director.

Netherlands Cancer Institute: Dr. H.R. Roos, Group Leader; Mr. M.G.O.M. de Haas, Administrator.

Companies

Gist-Brocades: Dr. N.W.F. Kossen, Associate Director of R&D.

Heineken: Dr. B.W. Drost, Director of Research.

Unilever: Mr. R. Keuning, Member of the Board of Directors, Unilever Research Laboratory.

AKZO Pharma: Dr. W. Smit, Member of the Board of Management.

Coopers and Lybrand: Peter B. Peart, U.S. Audit Consulting Partner.

SECTION E

BIOTECHNOLOGY IN NORWAY, FINLAND, & DENMARK

SUMMARY

Biotechnology activities in Norway, Finland, and Denmark are sharply limited by the size of their research establishments and their industrial bases. The most important efforts are in industry, where a number of pharmaceutical and specialty chemical companies have been highly successful in the past, and are introducing the new technologies of genetic engineering and monoclonal antibody production.

Finland has a novel technology transfer institution, the Recombinant DNA Laboratory, funded by the government, university, and industry. It also has two major corporations, ALKO (the state alcohol monopoly) and Kemira (the chemical company), which have been exploring the potential uses of biotechnology.

The Danish scientific infrastructure is considered weak in both research and education. The government has proposed an Action Program in Biotechnology that would increase research funding. At the same time, more stringent legislation governing industrial applications of recombinant DNA technology has been passed. Novo Industri is also the world's largest producer of industrial enzymes. Carlsberg Biotechnology is a new company started by the Carlsberg Laboratories, a major research establishment.

I. NORWAY

[There was no attempt made to conduct a study of biotechnology in Norway, but participation in a Symposium on "S-Adenosylmethionine as a Model System for Drug Design" held in Bergen, Norway, June/July 1985, provided an opportunity to discuss the Norwegian situation with local scientists. A meeting at the American Embassy in Oslo provided some additional background.]

At the present time, there is no national biotechnology program in Norway, but departments at the universities of Oslo and Bergen were in active competition to set up biotechnology programs. It had been anticipated that some of the oil revenues would be set aside for investment in the infrastructure of the country and/or investment in new high technology industries as the key to the economic future. The latter approach had been implemented, in part, focusing on deep sea technology, in which the Norwegians had made significant progress. Biotechnology is one of the new technologies of interest to the Norwegians. The recent change in government, however, combined with the severe recession brought on by the slump in oil prices, make it unlikely that there will be any new government initiatives to foster biotechnology.

II. FINLAND

Finland is a small country of 4.8 million people, with a prosperous, modern economy heavily dependent upon exports, and whose major industrial sector is lumber and wood products. The most important biotechnology activities are located at the Recombinant DNA Laboratory at the University of Helsinki, and at the Kemira and ALKO companies.

The Recombinant DNA Laboratory: The importance of genetic engineering was first recognized in 1980 by the Finnish National Fund for Research and Development (SITRA), which supported a 3-year, $1 million dollar project, carried out at the Meikahti Institute and the National Health Institutes. This project was directed by Dr. Leevi Kaariainen (1). In June 1982, the decision was made to create a new Recombinant DNA Laboratory at the University of Helsinki. This laboratory represented an unusual consortium between the university, the government, and industrial firms (2).

The participants in this new enterprise were the Academy of Finland, the Ministry of Education, SITRA, and a new company, Genesit. The building was provided by the University, SITRA provided most of the equipment, the Academy of Finland supports three academic positions assigned to the Laboratory, and NESTE Petroleum Company, along with Kemira Company, funds the position of the director. Most of the operating costs are provided by Genesit, whose shareholders are: the Finnish State Alcohol Company (ALKO), Farmos Group Ltd., NESTE Petroleum Ltd., Orion Corporation, the Finnish Sugar Company, and the Finnish Cooperative Dairies Association (VALIO) (2). The director of the Laboratory is directly responsible to the general administration of the university. In mid-1985, the staff numbered 40, of whom 25 were scientists and 15 were technical support staff. It was expected that the number of staff would peak at 50 (1).

The Laboratory was conceived primarily as a research center with current research programs in the following areas (2):

I. Structure and physiology of enveloped viruses

   a. Structure and biosynthesis of Semliki Forest Virus
   b. Biogenesis of Uukunami Virus, and
   c. Synthesis of Rubella Virus structural proteins

II. Expression of foreign genes in B. subtilis.

III. Construction of recombinant DNA (rDNA) molecules for expression in yeast, and

IV. Developmental studies in Drosophila.

In the near future, the Laboratory expects to initiate programs in (a) screening of genetic diseases in Finland and (b) development of gene expression systems in animal cells.

The project areas cover a number of important research questions, covering the full spectrum from bacterial membrane transport through virology, to developmental biology. Work on the Semliki and Uukunami viruses is unique to Finland, and bears some relevance to forestry. The keystone of the Laboratory is the Bacillus project under Dr. Iilka Palva, a highly respected bacterial geneticist. Presently, foreign genes can be expressed in B. subtilis, but the foreign proteins are produced in low yield, presumably due to protease activity. A solution to this problem could make Bacillus the system of choice for industrial production of many proteins, since they would be exported out into the growth medium (see following section on ALKO). The development of yeast and animal host-vector systems for gene expression are consistent with making available alternative production systems. Protein and DNA sequencing, as well as the computer programs for their analyses, are well established. One of the responsibilities of the laboratory is the offering of two genetic engineering courses during the year, a basic and an advanced one.

It was apparent that the laboratory had been established both as a research organization and as a national resource, albeit limited in size. The companies in Genesit have the option to develop and commercialize any research findings. This has been done in at least one instance. One severe gap in the makeup of the Laboratory is the absence of any research in plant molecular biology, a high priority area for a country such as Finland. A plant group had been established under the leadership of Dr. Tapio Palva (brother of Dr. Iila Palva) in the Department of Genetics. It was envisioned that this group would be incorporated into the Laboratory. Unfortunately, the group was lured away to Sweden, by the offer of better facilities and more extensive resources (1).

KEMIRA COMPANY is the largest chemical company in Finland, and produces fertilizers, pesticides, industrial chemicals, textile fibers, and titanium. Net sales for 1984 amounted to Finnish marka (FnMk) 4,684 million (approximately $780 million), of which approximately 50 percent were export earnings. Export sales were projected to rise to 60 percent in 1985. Fertilizers and pesticides accounted for half of Kemira's business, and 2.9 percent of sales are spent on R&D. Kemira is totally owned by the Finnish government (3).

During the early months of 1985, Kemira reevaluated its business strategy, as it attempted to assess the impact of biotechnology on its traditional and highly profitable operations. The current view is that biological fertilizers and pesticides are not more efficient, nor cheaper, and therefore, are unlikely to take over more than 5-10 percent of this market. Political considerations, and of scientific breakthroughs (e.g., development of new crop strains that require less fertilizer) could seriously alter the situation. Kemira has adopted an aggressive, defensive strategy, that emphasizes basic research in plant physiology and molecular biology, with the adoption of any possible applications. Its first steps were:

(1) Participation in the establishment of the Recombinant DNA Laboratory at the University of Helsinki. The failure of the Laboratory to set up a research program in plant biology apparently resulted in Kemira not becoming a shareholder in Genesit (4).

(2) Creation of a biotechnology division and a plant physiology research group, with a staff of 10, at their Espoo research center. One key question under study is the process by which plants use fertilizers. A second research area benefits from previous empirical experience on biological methods of pest control. Two systems have been developed and are in use: one uses a polyhydroxis virus to kill the mites that infect Finnish forests; the other is still confidential, and uses a bacterial strain to control fungal diseases of crop plants. Characterization of such agents is only the first step, as they have narrow host ranges, and are sensitive to a wide variety of external conditions (e.g., temperature, pH, humidity). The use of rDNA technology could improve the efficacy of such agents (4).

(3) Purchase of stock in Calgene, an American plant biotechnology firm. The first project was characterization of a herbicide-tolerant turnip rape plant (3).

(4) Development of joint research programs with the Max Planck Institute for Plant Breeding (Cologne, German Federal Republic) and the University of Ghent in Belgium (4).

Kemira's current effort is an exploratory one, prior to making more serious and long-term commitments. Given the difficulties of establishing research in plant biology at the Laboratory of Recombinant DNA, it is probable that there will be an expansion of joint efforts with foreign companies and institutes.

The Finnish State Alcohol Company (ALKO) is a government-owned company, whose main products are potable alcohol (primarily vodka) and beer. It also has a monopoly on the import and sales of alcoholic beverages. ALKO's sales in 1984 totalled FnMk 7,121 million (approximately $1,186 million), with net profits of FnMk 710 million ($118 million). ALKO provides the Finnish government with 10 percent of its annual budget (5).

The main reason for visiting ALKO, was to look at the impact of modern biotechnology on a traditional industry (i.e., fermentation). One of the first biotechnology projects involved alpha-amylase, which is used industrially to break down starch as an early step in fermentation. The enzyme from B. licheniformis is thermostable, which makes it an excellent candidate for industrial applications. It is produced, however, at low levels in the parent organism. Using rDNA techniques, the synthesis of this enzyme can be increased 500-fold. Research on this project was carried out by Dr. Palva's group, at the Recombinant DNA Laboratory, under the terms of an agreement with Genesit. Subsequently, ALKO acquired the strain from Genesit (6).

ALKO has also carried out some interesting cost analyses of the introduction of new, genetically engineered organisms into the fermentation processes. Though most of the results are confidential, Dr. K. Erikkson, Director of Production and Research, presented a paper at the U.N. Conference in Szeged, Hungary. His data showed that the increased efficiency of fermentation by a new genetically engineered yeast strain was offset by the

cost of changes in downstream processing. Ultimately, the engineering and processing costs are much more important than changes in the characteristics of the microorganisms. It appears that ALKO has developed an effective cost analysis system to define the economic advantages, and disadvantages, of using rDNA organisms in standard processes.

As a matter of social policy, ALKO cannot increase its sales in Finland (which would exacerbate already serious problems with alcoholism). Under the circumstances, further growth would require the establishment of new business areas. Traditionally, ALKO has produced industrial enzymes for in-house use. The Board of Directors has, under active study, a proposal to combine current R&D in genetic engineering and traditional fermentation technology for production of industrial enzymes for the world market. The final decision is expected to be made in the near future.

III. FINLAND AND NORWAY: CONCLUSION

Finland and Norway share certain characteristics. They are both small and prosperous Western countries, with modern economies that are heavily dependent upon exports and technology-intensive industries. Neither has a history of research in molecular biology, nor do they have national policies for the development of a biotechnology industry. Having said this, it must be noted that in such countries (this is also true of Western Europe as a whole), no sector is free of government intervention. Even the private sector has a large component of companies that are wholly, or partly, owned by the government.

In Finland, there may not be a national policy, but the small size of the scientific establishment and its close interaction with the various sources of funding, have resulted in a concerted effort, composed of three elements: the creation of a national research laboratory that serves as a national resource, the development of in-house biotechnology groups in two of the largest corporations, and the acquisition of technology through contracts and purchase of equity in foreign biotechnology firms. Kemira and ALKO are both profitable enterprises with significant cash reserves. Their biotechnology plans are likely to focus on areas in which they already have strong market positions and extensive downstream production experience. Norway is still at the starting line, but had hoped to use some of the funds from its North Sea oil revenues to follow the Finnish model of development. Both countries have some major liabilities, the most serious being the limited size of the scientific manpower pool and of the scientific research establishment. This forces the concentration of the available resources into a few specific areas. It also limits the upward mobility of bright, young scientists. Larger countries with abundant resources and a more favorable research environment, can successfully recruit away key groups (as in the case of Dr. Tapio Palva and his group). One possible option would be to increase international collaboration, particularly among the Scandinavian countries. There is no evidence of this, except at the purely individual, scientific level. Another option is to acquire technology through contracts, joint ventures, and acquisition. There is considerable interest in this approach, and much of it is centered around the U.S. biotechnology industry.

This latter point is one that recurs, over and over: the sale of U.S. technology as a growing trend in our international trade. The extent, terms, and strategies, of such transactions have serious implications, not only for individual companies, but also for U.S. policy as a whole.

IV. DENMARK: INTRODUCTION

Denmark has an important agricultural sector, as well as manufacturing industries in furniture, textiles, and metals. Like many other European countries, the economy has been plagued with high inflation, high interest rates, large government deficits, and severe unemployment. A center-right coalition government was elected in 1982, and its economic policy has had major successes in reducing both inflation (4.7 percent in 1985) and interest rates. The unemployment rate of 9.3 percent is the lowest in the European Economic Community (EEC) after Luxembourg. The one problem that has not responded to government efforts has been the negative trade balance that reached 4.5 percent of GDP in 1985 (7).

Trade between the U.S. and Denmark covers a fairly narrow range of products, with Denmark selling $1.7 billion to the U.S., while U.S. exports to Denmark were valued at $1.1 billion in 1985. Danish exports included meat and meat products, furniture, windmills, raw furs, butter cookies, insulin, and enzymes. U.S. sales to Denmark were coal and coke, commercial aircraft, computer equipment, military equipment, and tobacco (7).

Danish industry is characterized by the small size of many of its companies. More than 6,000 companies have between 5 and 500 employees, while only 80 companies have more than 500 employees (8). The small scale of Danish industry, and its strong dependence on new technologies, has encouraged active cooperation between government and industry in industrial innovation.

[Time constraints, scheduling problems, and a lack of documents translated into English, have not permitted a comprehensive study of biotechnology in Denmark. Following the advice of several experts, most attention was focused on several important companies and on the role of government in technology transfer.]

V. DENMARK: GOVERNMENT POLICY

Danish science policy places strong emphasis on technology transfer and industrial innovation. The three most important organizations are the Danish Research Agency, the Council of Technology, and the Academy of Technical Sciences. The first is responsible for basic research, and the other two for applied research and development.

The Danish Research Agency (DRA) is an agency of the Ministry of Education, with a staff of 75. It provides the administrative infrastructure for the six research councils and for the Council of Research Policy and Planning. In addition, it is responsible for Danish participation in international research programs.

The Council of Research Policy and Planning is responsible for advising the government and parliament on science policy, promoting the application of Danish research, and overseeing the research and budgets of the individual research councils.

There are six research councils: the Science Research Council, the Medical Research Council, the Agricultural Research Council, the Social Science Research Council, the Cultural Arts Research Council, and the Technology Research Council. The DRA does not maintain any laboratories of its own, though some of the research councils do support a small number of research groups. The DRA primarily funds basic research at universities and public research institutes (accounting for 85 percent of research grants) (9).

A limited amount of funding is, however, provided to these technological research institutes which are affiliated with the Academy for Technical Sciences and also have strong industrial ties. A new program for basic research associated with new technologies was established in 1985, with a 5-year budget of Dkr 300 million ($28.3 million)*. An additional Dkr 33 million ($3.11 million) will be spent over the same period for biotechnology research. Table 1 summarizes the budgets of the DRA and the six research councils. Biotechnology-related research is supported by the DRA, the Science, medical, Agricultural, and Technology Research Councils and is estimated to total Dkr 50-60 million ($4.7-$5.7 million) (10).

The National Agency of Technology is part of the Ministry of Industry and carries the responsibility of administering seven industrial promotion schemes (11). These are: the Council of Technology, the Productivity and Consultancy Scheme, Industrial Research and Development Fund, Product Development Scheme, Industrial Liaison Council, National Testing Board, and the National Council of Metrology.

The annual budget of the National Agency of Technology is Dkr 1.1 billion ($103.8 million). The three principal schemes involved in support of biotechnology projects are the Council of Technology, the Industrial Research and Development Scheme, and the Product Development Scheme. The Council of Technology is responsible for planning and evaluating the applications of new technologies, as well as for providing financial support to technological service institutes and R&D projects. This support usually takes the form of 3-year contracts covering 25-30 percent of the research costs. The budget for 1985 was Dkr 356 million ($33.6 million). If one accepts a stringent definition of biotechnology, the annual support in this sector is approximately Dkr 10 million ($0.94 million). The Industrial R&D Fund provides loans for research that leads to new products or processes. These loans cover 50 percent of the costs (or 75 percent in the case of small companies), no interest is charged during the initial production phase, and subsequent interest charges are at the official discount rate, commencing 2 years after completion of the development period. If the project fails, the loan is written off. The budget for this scheme in 1985 was Dkr 232 million ($21.9 million) (11)(12).

*Average exchange rate for 1985: Danish krone (Dkr) 10.596 = $1.

Table 1.

Science Budgets

	1985 Budget (Dkr)	Estimated Biotechnology Expenditures (Dkr)
Danish Research Agency	273.8M ($25.8M)*	
The Research Councils		
The Science Research Council	51.2M ($4.8M)	
The Medical Research Council	43.4M ($4.1M)	50-60M ($4.7-5.7M) (DRA & Research Councils)
The Agricultural Research Council	23.4M ($2.2M)	
The Social Science Research Council	25.6M ($2.4M)	
The Cultural Arts Research Council	25.6M ($2.4M)	
The Technology Research Council	27.8M ($2.6M)	
National Technology Agency		
Council of Technology	356M ($33.6M)	10M ($0.94M)
Industrial R&D Fund	232M ($21.9M)	not available
Product Development Scheme	113M ($10.7M)	20-25M ($1.9-2.4M)

*Average exchange rate for 1985: Dkr 10.596 = $1.
M = millions

The Product Development Scheme is primarily directed towards innovation in existing products and processes. This is done through grants, which cover up to 40 percent of the costs. The budget for 1985 was Dkr 113 million ($10.7 million), of which Dkr 20-25 million ($1.9-$2.4 million) was spent on Biotechnology projects (12).

The Action Plan in Biotechnology (10) has been proposed by the present conservative government following the realization that Denmark might be falling behind in biotechnology with serious effects on its pharmaceutical and food industries. A special panel identified a number of research priorities that are of importance ot the Danish economy. These are: fundamental research in molecular and cell biology and immunology, plant and fish biology, diagnostics and vaccines, food processing technology, fermentation and downstream processing. The proposal has a budget of Dkr 500 million ($47.2 million) for the 5-year period of 1986-90. Approximately 80 percent of the funds are earmarked for the development of biotechnology research centers with a focus on the priority areas. Plans are currently under way to establish science parks in conjunction with the Universities of Copenhagen and Aarhus. The initial budget for 1987 would be Dkr 75 million ($7.1 million). It is believed that the chances for passage of this Action Program are good, though there is no guarantee that the full budget will be approved. Table 1 indicates that the amount currently being spent on basic biological research is probably equivalent to that allocated for technology transfer and industrial innovation. The Action Program would more than double the amounts now available from the DRA and the research councils. It is felt that these resources would go primarily for building up the research base in the universities and public institutes and bring them up to international standards. Under the circumstances, it is not likely that there would be sufficient resources for expanding industrial innovation schemes.

New Legislation for Control of Biotechnology (13): During the past 10 years, regulation of biotechnology in Denmark has been based variously on the Environmental Protection Act, the Chemical Materials and Products Act, the Conservation of Nature Act, and the Foodstuffs Act. On May 30, 1986, the Danish parliament approved comprehensive legislation to regulate the application of biotechnology (defined on the basis of recombinant DNA and hybridoma technologies). The Ministry of the Environment (MOE) is charged with the enforcement of the new regulations. Several measures have generated serious concern: genetically engineered plants cannot be released into the environment, even for experimental purposes, requirements for approval by the MOE for a number of industrial activities involving rDNA technology, and requirement for approval by county councils of production involving genetically engineered organisms. Though the regulations are not unreasonable, it is feared that the MOE might lack the scientific expertise to assess many of the new processes, and that delays in obtaining approval might interfere with the competitiveness of Danish industry. The present regulatory legislation has been approved at the same time that the government has proposed a new Action Plan for strengthening the infrastructure in biotechnology, and promotion of new industrial activities. There is, however, no evidence of any coordination between these two measures and this might ultimately lead to their acting at counterpurposes.

VI. DENMARK: UNIVERSITIES & RESEARCH INSTITUTES

Basic research in Denmark is centered around the universities and is funded through a dual support system. Universities are funded directly by the Ministry of Education which provides for faculty salaries and overhead costs only. Research expenses and additional personnel costs are provided for by the DRA and the research councils. Denmark has five universities, a technical university, an agricultural university, and a school of Pharmacy. The primary biological research groups are located in the Royal Institute of Technology and the Universities of Copenhagen and Aarhus. The view was frequently expressed that university research was underfunded and understaffed, therefore providing a weak base for technology development.

The Academy of Technical Sciences (ATV) is a private, non-profit organization primarily funded by industry for the purpose of providing R&D services to the community, trade, and industry. There are 19 ATV affiliated institutes with a total staff of 1,250 employees and an annual budget of Dkr 450 million ($42.5 million), of which 20 percent was contributed by the government. The principal institutes with biotechnology activities are the Biotechnical Institute, the Jutland Technological Institute and the Technical Institute.

VII. DENMARK: INDUSTRY

Biotechnology in Danish industry is concentrated in the pharmaceutical and food sectors. Novo Industri and Nordisk Gentofte are both major producers of insulin, while Carlsberg Biotechnology is an offshoot of the famous Carlsberg Laboratories. Their strong financial and technical resources make these companies a key element in Danish biotechnology.

NOVO INDUSTRI is the largest biotechnology company in Denmark, and is a multinational group with subsidiaries in 22 countries. Annual sales in 1985 were $535 million, with a net profit of $78.4 million (see Table 2). Ninety-eight percent of Novo's sales were outside of Denmark. It is composed of two major operating divisions: Pharmaceuticals and Enzymes, which account for 59 percent and 40 percent of sales respectively. Novo has 39 percent of the world insulin market and 50 percent of the industrial enzyme market (14).

The Pharmaceuticals Division has one major product, insulin, which accounts for 80 percent of its sales. Novo has 39 percent of the world insulin market as compared with 41 percent for Eli Lilly and 11 percent for Nordisk Gentofte. Its market position was challenged by the introduction of genetically engineered human insulin by Eli Lilly, but Novo is now able to market its own form of human insulin produced by modification of the bovine hormone. Novo has also developed its own genetically engineered insulin which is produced by yeast fermentation, and has built a plant for manufacture in Klundborg. Operation of this facility has been delayed by litigation related to the use of rDNA microorganisms (15).

The Enzyme Division focuses on industrial applications, and the principal markets are: food industry (amylases, proteases, cellulases, pectinases);

Table 2.

Characteristics of Companies

	Novo Industri	Nordisk Gentofte	Carlsberg Biotechnology
Sales (Dkr)	4,118M ($388.6M)* (+9%)	809M ($76.3M)	N/A
Net Profit (Dkr)	604M ($57.0M) (-12%)	75M ($71.0M)	None
R&D Budget	453M ($42.7M)	84M ($7.9M)	N/A
Major Products	Insulin Heparin Industrial enzymes: proteases carbohydrate enzymes lipases Monoclonal Antibody Kits	Insulin Human Growth Hormone Factors VIII & IX Albumin Gamma-globulin	LH-RH TRH Somatostatin Oxytocin Encephalin
Current Research Projects	Blood Coagulation Factors Biological Peptides with cardiovascular & anti-inflammatory activities New enzymatic processes		
Joint Ventures with U.S. Companies	Squibb-Novo: new company established with Squibb Joint R&D with Zymogenetics Equity in Zymogenetics	Chiron: contract R&D insulin Chiron: joint R&D Factor VIII	

*Average exchange rate for 1985: Dkr 10.596 = $1.
M = millions

detergent industry (proteases, amylases); and starch industry (glucose isomerase, amylases, glucosideases).

The enzyme production facility outside Copenhagen is considered to be one of the most modern of its kind in the world. The enzyme R&D facility is designed for process development and pilot production of industrial quality material.

One important aspect of enzyme research is its formulation, which serves to maximize the activity and stability while minimizing potential allergic reactions to the purified protein (e.g., immobilized or granular enzymes).

Novo is a good example of a medium-sized, multinational company with a successful record in its two major product areas. It is increasingly exposed to international competition and it is unlikely that sales of its present products will increase significantly. Novo has made a number of important moves:

(1) Development of new products: In enzymes, besides conducting research into products with improved activity, stability, and reaction conditions, Novo is trying to find new applications in production technology. Among others, there is the increased use of proteases in the food industry, and the use of lipases for production of lipids and esters in the chemical industry. In pharmaceuticals, there is research into coagulation factors (joint R&D with the U.S. firm Zymogenetics for production of Factor VII) and biological peptides with cardiovascular or anti-inflammatory activities.

(2) Development of new business areas: Novo BioLabs is developing monoclonal antibody kits for diabetes, and also enzyme reagents for laboratory use. Novo Diagnostic Systems is producing brain scanners and blood flow monitors. The Alfred Jorgensen Laboratory for Fermentation provides consulting services for the wine, brewing, and food industries.

(3) Expansion abroad: The U.S. is one of Novo's most important markets, and one that has large growth potential. The capacity of the enzyme production plant in Franklinton, N.C., has been doubled, and there is an R&D laboratory and pilot plant in Wilton, CT. A new company, Squibb-Novo, has been formed with Squibb to market insulin in the U.S. and Squibb products in Denmark and Norway. Novo has also invested in Zymogenetics (see above). A new enzyme production facility in Hokkaido, Japan will be completed in 1988. Novo Industri stock is traded both on the London and New York stock markets.

The NORDISK INSULIN-LABORATORIUM (16) is composed of three separate units: Nordisk Gentofte--production and sales; Steno Memorial Hospital--treatment of and research into diabetes and other endocrine diseases; and Hagedorn Research Laboratory--basic research into diabetes.

The Nordisk Insulinfond is a non-profit foundation that receives a proportion of the profits of the Nordisk Insulin-Laboratorium, plus income

from its endowment. These funds are used to support medical research in Scandinavia. In August 1986, Nordisk Gentofte launched a share issue on the Copenhagen Stock Exchange in order to raise Dkr 180 million ($16.9 million) (17). Nordisk was established in 1925 by a group that had left the Insulin-Laboratorium. This resulted in prolonged litigation between the two organizations. (The characteristics of the company appear in Table 2.)

Insulin accounted for 85 percent of total sales in 1985, and 90 percent of insulin production was exported. The other products are obtained by extraction from natural sources: human growth hormone from human pituitaries, and Factors VIII and IX, albumin and gamma-globulin from human blood. Nordisk produces porcine insulin, but it has now developed an enzymatic substitution of a single amino acid to convert it to human insulin. Nordisk has entered into an agreement with Wellcome to produce insulin in Wellcome's U.K. facilities. There is now increasing concern about possible contamination of human growth hormone by Kreutzfeld prions and of Factor VIII by AIDS virus. This has stimulated R&D into genetically engineered human growth hormone (presently in clinical trials), insulin, and Factor VIII (this last in collaboration with the U.S. company, Chiron) (18).

United Breweries is one of the largest breweries in the world and owns both Carlsberg and Tuborg. It also established Carlsberg Laboratories, a major center for microbiological research. Using some of the methods developed there, United Breweries created a new biotechnology company, CARLBIOTECH, with an initial capitalization of Dkr 15 million ($1.4 million) and a staff of 40 (see Table 2). Carlbiotech has combined two technologies for the large-scale production of biologically active peptides: enzymatic synthesis by reversal of protease reactions and the use of large-scale HPLC for peptide isolation. This enables them to produce peptides of 30-40 amino acids routinely. Carlbiotech markets some of its own products, as well as producing under contract with major pharmaceutical companies. They have a subsidiary in Australia called Peptide Technologies, which is 48 percent owned by Carlbiotech. It is expected that they will begin to show a profit within the next 2 years. As their business expands, they intend to find a partner in the U.S. to develop that market further (19) (20).

INDUSTRIAL OVERVIEW

Novo and Nordisk have been remarkably successful in establishing profitable niches in insulin and industrial enzymes. They have been active in developing new formulations and production technology to retain their competitive edge. Both have been relatively slow in introducing rDNA techniques into their operations, and in developing new products.

The Danish biotechnology industry faces certain major difficulties. One is a weak scientific infrastructure that limits the amount of basic research available. The larger companies do their own targeted research and train their own scientific staff. Another serious problem is political opposition to rDNA work, which has led to the present regulatory legislation. In addition, both individual and corporate taxes are high (the latter having been increased from 40 percent to 50 percent). In the past, the need for basic

research was not so strongly felt, but this has begun to change, along with the establishment of production facilities outside of Denmark (which could be used for manufacture of rDNA products if the regulatory process becomes too restrictive). It is important to remember that the Danish companies have limited resources, e.g., Novo is the largest Danish biotechnology company, but is only a medium-sized company on a global scale. Though there is a great deal said about Nordic cooperation, there was little evidence of this. Major research contracts and joint ventures were with firms and organizations outside the Nordic bloc (frequently in the U.S. and U.K.).

VIII. DENMARK: CONCLUSION

The Danish government has become increasingly aware of the industrial importance of biotechnology. Its present expenditures in this area are limited (probably less than $20 million per year), but it is attempting to increase this by passage of a new Action Program in Biotechnology. This would not only increase the amount of funding available, but would focus it in a selected number of priority areas. Denmark has also been an active participant in European programs, such as the European Molecular Biology Organization, and the Biomolecular Engineering and Biotechnology Action Programs of the EEC.

Some of the most important resources in Danish biotechnology are in the private sector, in both the private research foundations and companies. They have been successful in developing and exploiting specific research areas and technologies independently of the activities in the universities. There is increasing industrial concern that the research base is not large enough at a time of expanding foreign competition and there is doubt that the Action Program will dramatically change that situation. Industry is even more concerned about environmentalists' opposition to production of rDNA products, and the imposition of new regulations. This has led both Novo and Nordisk to position themselves so that they can manufacture outside of Denmark if necessary. At the same time, both companies have to develop new series of products in order to remain competitive. Carlbiotech is one of the few new biotechnology companies in Scandinavia, and is trying to apply its new technologies to a whole range of both established and new products. In so doing, it is trying to carve out an international market niche in the same manner that Novo and Nordisk had done before it.

ACKNOWLEDGMENTS

Max Miles, Commercial Counselor, Foreign Commercial Service, American Embassy, Copenhagen.

REFERENCES

1. Kaariainen, Leevi, Director, Recombinant DNA Laboratory, personal communication, June 1985.

2. Recombinant DNA Laboratory, Annual Report, 1984.

3. Kemira Annual Report, 1984

4. Tinnila, Aulis, Director of Biotechnology, Kemira, personal communication, June 1985.

5. ALKO Ltd., Annual Report, 1984.

6. Vaisanen, Eino, Microbiologist, ALKO, personal communication, June 1985.

7. Foreign Economic Trends Report, American Embassy Copenhagen, April 1986.

8. Technological Service Institutes in Denmark, Ministry of Industry, December 1983.

9. Science Agency Profile: Denmark, American Embassy, Copenhagen, October 1984.

10. Olesen Larsen, Dr. Peder, Danish Council for Research Policy and Planning, personal communication, August 1986.

11. National Agency of Technology, October 1985.

12. Rubin, Jan, and Inger Petersen, National Agency for Technology, personal communication, August 1986.

13. New Danish Biotechnology Regulations, translation by American Embassy Copenhagen, June 1986.

14. Novo Industri, Annual Report, 1985.

15. Lassen, Ulrik V., Novo Industri, personal communication, August 1986.

16. Nordisk Gentofte, Annual Report, 1985.

17. Financial Times, August 21, 1985.

18. Hansen, Bruno, Hagedorn Research Laboratory, personal communication, August 1986.

19. Carlbiotech, 1986.

20. Johansen, Jack T., Carlsberg Biotechnology Ltd., personal communication, August 1986.

APPENDIX

INDIVIDUALS AND ORGANIZATIONS VISITED

GOVERNMENT

National Agency of Technology: Mr. Jan Rubin, Engineer, and Mrs. Inger Petersen, Chemical Engineer, Research Department.

Danish Council for Research Policy and Planning: Professor Peder Olesen Larsen, Chairman.

INDUSTRY

Kemira Oy: Dr. Aulis Tinnila, Director of Biotechnology; Heikki Rosenquist, Director of Research Center; Alpo Aapola, Senior Research Scientist, Department of Biological Research.

ALKO Oy: Dr. Kalerro Eriksson, Director of Production & Research; Eino Vaisanen, Microbiologist.Novo Industri: Professor Ulrik Lassen, Senior Executive Vice President, Chief Science Officer; Mr. Knud Aunstrup, Vice President, Enzymes R&D.

Nordisk Gentofte: Dr. Bruno Hansen, Vice President.

Carlsberg Biotechnology Ltd.: Dr. Jack T. Johansen, President.

RESEARCH INSTITUTES

Recombinant DNA Laboratory: Dr. Leevi Kaariainen, Director; Dr. Ilkka Palva, Ph.D.

University of Helsinki: Dr. H. Gyllenberg, Department of Microbiology.

SECTION F

BIOTECHNOLOGY IN SPAIN

SUMMARY

The Spanish government has initiated a Mobilization Program in Biotechnology. This involves the creation of a National Center of Genetic Engineering and Biotechnology, a reorganization of government supported research, and support of industrial biotechnology projects. Though starting from behind, Spain counts with a solid nucleus of excellent researchers and a positive, rapidly changing business environment. There is widespread interest in collaboration with U.S. biotechnology companies.

I. INTRODUCTION

Spain is one of the less affluent countries in Western Europe. Its economy has traditionally been dependent on the agricultural sector, tourism and certain manufacturing industries (e.g. automobiles). During the past few years, the Spanish economy has suffered from poor growth, high inflation and severe unemployment. The Socialist government of Felipe Gonzalez has managed to bring inflation under control and produced a real growth rate of 2.2 percent in 1985. However, unemployment remains at a high level of 20.6 percent (1).

The Spanish government initiated a program of massive industrial reconversion in 1982. Its purpose has been to consolidate and modernize Spanish industry. In principle, this should make Spanish industry more competitive and create new jobs. Overall unemployment has been exacerbated by layoffs in traditional industries, e.g. steelmaking and shipbuilding. An important aspect of the industrial reconversion policy is the selection of high priority areas, followed by government funding of R&D and support for technology transfer from research laboratories into the industrial sector. Two of the key target areas in new industries are microelectronics and biotechnology, the latter receiving formal recognition in a National Mobilization Program in Biotechnology which is now being put into place. U.S. support for basic research in Spain as well as the training of significant numbers of Spanish researchers in the U.S. has contributed to the development of Spanish biotechnology.

[In order to evaluate the Mobilization Program and the state of biotechnology in Spain, fourteen meetings were held with key Spanish scientists, government officials and industrial managers.]

II. GOVERNMENT POLICY

Spain began its move into biotechnology at a significant disadvantage. In order to reach the level of its European neighbors, it has had to reform and strengthen its scientific infrastructure, expand its funding of R&D and increase its pool of biological scientists and engineers.

The Spanish government has acted to meet this challenge in two ways: the creation of a Mobilization Program in Biotechnology and the recent passage of a new law on Promotion and Coordination of Scientific and Technical Research. In 1983, the Spanish government announced the objectives of the Mobilization Program, which were to provide support for basic and applied research and to establish appropriate mechanisms for the transfer of new technologies to the industrial sector. The formulation and implementation of scientific policy is also being restructured. Though a number of ministries are concerned with biotechnology, the Ministry of Education and Science, and the Ministry of Industry and Energy provide 70 percent of the research funding and most of the infrastructure (2). Table 1 summarizes the key agencies and their respective roles. (The most significant changes brought about by the new legislation will be indicated at the end of this section.)

Directorate General of Scientific Policy (Direccion General de Politica Cientifica): This department of the Ministry of Education and Science is responsible for development, coordination and administration of science policy. Research in Spain is primarily conducted in government institutes, medical centers and, to a much lesser degree, in universities.

The Advisory Commission on Scientific and Technical Research (Comision Asesora de Investigacion Cientifica y Tecnica, CAICYT): This body has two important functions: scientific review and funding of research grants. In addition, it serves as a technical advisory panel to other government agencies. Through its application of peer review, it has revolutionized the manner in which scientific research is conducted in Spain. Its budget of approximately $88 million covers all scientific disciplines, with around 5 percent going for biotechnology (2). The CAICYT funds three kinds of projects:

(a) Research projects carried out in government research institutes and in universities.

(b) Applied research projects (Planes Concertados) which can fall into two categories. In the case of industrial R&D projects, the government funds up to 50 percent of the cost of the project, with the company putting up the other 50 percent. If the project fails, the government writes off the loan. If it is successful, the loan has to be repaid over a period of 5 years without any interest (2). In the case of coordinated projects (Planes Concertados-Coordinados), collaboration between a company and a government or university research laboratory is established. The CAICYT lends an amount equal to that of the industrial contribution and up to 100 percent of that from the government laboratory. Therefore, the industrial commitment is only 25 percent of the total (2). The conditions for repayment are similar to those for the industrial R&D projects mentioned above.

(c) Special Programs: Mobilization Programs fall into this category and they are designed to stimulate R&D in priority areas such as biotechnology.

Table 1.
PRINCIPAL SCIENTIFIC AGENCIES

Agency	Advisory Commission on Scientific & Technical Research (CAICYT)	Higher Council for Scientific Research (CSIC)	Center for Development of Industrial Technology
Coordinating Body	Department of Scientific Policy	Department of Scientific Policy	
Functions	Scientific review Research funding	Operation of government research institutes Research funding Training programs Establishment of National Biotechnology Center	Assessment of R&D projects Funding R&D projects of industrial relevance
Budget*	Ptas 15bn ($88.2M)	Ptas 20bn ($117.6M)	Ptas 5bn ($29.4M)

*1985 average exchange rate: $1 = Ptas 170.04.
M = millions, bn = billions

Higher Council for Scientific Research (Consejo Superior de Investigaciones Cientificas, CSIC): Most scientific research in Spain is carried out in CSIC institutes and laboratories. The CSIC has an overall budget of approximately $118 million. (This does not cover all of the operating costs of its laboratories (3), a substantial part of which is provided by grants from the CAICYT. The costs include 67 percent for salaries, 10 percent for overhead, and 23 percent for operating expenses.) The major research sectors funded by the CSIC are: agriculture (16%), applied physics (15%), chemistry (17%), biology and medicine (18%), and humanities (7%). The remainder is in mathematics, earth sciences and technologies. Approximately 25 percent of research in biology/medicine falls into the category of biotechnology.

The CSIC is presently undergoing a rapid expansion with 350 new positions being created last year and 200 this year. The CSIC currently has a staff of 6,000, of which 2,000 are Ph.D.'s and 800 are students (3). Projects carried out in the CSIC institutes are individual or coordinated amongst several groups. Since the most important part of the funding for the institutes comes from CAICYT, the arrangements described for CAICYT above are also valid there. In addition, private industry can contract research out to the CSIC institutes.

Center for Development of Industrial Technology (CDTI) is a legally autonomous agency of the Ministry of Industry and Energy, established to promote technological innovation in Spanish industry. It provides four types of financial support:

(a) Risk and venture capital with CDTI sharing in the profits resulting from the project.

(b) Risk capital involving only financing of the project.

The reimbursement plan for these two capital schemes is dependent on sales and is carried out over a period of 2 to 6 years and, a fee of 9-13 percent (4).

(c) Investment: CDTI purchases stocks or bonds in high technology companies on a minority basis and with the intention of eventually selling its stake.

(d) Privileged credits: these are used to fund technological projects, and also have payback requirements similar to those indicated above.

The first two mechanisms are directed towards innovation while the third deals more with the creation of new industries. Privileged credits are frequently employed in the development of fairly low technology activities. CDTI's budget is approximately Ptas 5 billion ($29.4 million)*(4). CDTI will usually fund up to 30 percent of a new project to a maximum of Ptas 750 million ($4.4 million) (4).

*1985 average exchange rate: Spanish pesetas (Ptas) 170.04 = $1.

CDTI has carried out extensive studies of a number of high technology industries and has come to the conclusion that biotechnology was one of the areas in which Spain could find a profitable niche. At the end of 1984, CDTI had approved 89 projects overall with a total budget of Ptas 10.04 billion ($59.1 million), of which CDTI had invested Ptas 4.05 billion ($23.8 million). Biotechnology/medicine/chemistry accounted for 13 percent and agro-food for 10 percent of this budget (4).

CDTI is able to operate with a great deal of flexibility and speed since it is structured as a private company. It interacts closely with CAICYT and CSIC, from which it obtains technical advice, while it provides a mechanism for moving research developments into the industrial sector.

Fund for Public Health Research of Social Security (FIS), Ministry of Public Health and Consumer Affairs: This fund was created by agreement with the pharmaceutical industry. It is directed towards the funding of research in public health, training of personnel, fellowships, and travel grants. Its annual budget is approximately Ptas 1.1 billion ($6.5 million) (2). However, its involvement in biotechnology is fairly limited.

The Mobilization Program in Biotechnology: This was established in 1983 and, in its first phase, cover the period 1983-1986. It comprises three types of activities:

(a) the establishment of a National Center of Genetic Engineering and Biotechnology (henceforth called the Biotechnology Center),

(b) the training of researchers, and

(c) financial support for research and development.

The budget for the Program is given in Table 2. Of the figures provided for the Biotechnology Center, Ptas 700 million ($4.1 million) are designated for the Center's building and Ptas 1.5 billion ($8.8 million) for equipment (2). The Center will be staffed with 300 people, of whom 50 will be scientific researchers, 50 technicians, 50 support personnel, 20 administrative staff, 20 workers, 10 visiting faculty, and 100 students (both graduate and undergraduate) (2). Initially, research activities will be located in the building being constructed on the campus of the Autonomous University of Madrid. In later stages, other research units of the Center will be established in Barcelona, Sevilla and Valencia.

The Biotechnology Center will focus its basic research on the following areas: molecular genetics, immunology, industrial biochemistry, industrial microbiology, plant molecular biology and biochemical engineering. In applied research, emphasis will be placed on human and animal health care, agriculture and food processing, and waste treatment.

Given the special status of the Biotechnology Center, two separate committees have been given responsibility for its operations. A Board composed of representatives from the different Ministries as well as the CSIC will be responsible for policy and budgets. At the same time, a Scientific

Table 2.
BUDGET OF THE MOBILIZATION PROGRAM
(in pesetas)*

	1984	1985	1986	TOTAL
Training	50M ($294k)	60M ($353k)	70M ($412k)	180M ($1.1M)
Basic Research	---	90M ($529k)	100M ($588k)	190M ($1.1M)
Targeted Research & Industrial Projects	---	100M ($588k)	100M ($588k)	200M ($1.18M)
National Center of Genetic Engineering & Biotechnology	550M ($3.23M)	750M ($4.41M)	900M ($5.29M)	2200M ($12.9M)
Annual Totals	600M ($3.5M)	1bn ($5.88M)	1.17bn ($6.88M)	2.77bn ($16.29M)

*1985 average exchange rate: $1 = Ptas 170.04.
M = millions, k = thousands

Advisory Committee will work in collaboration with the CAICYT to develop and implement the scientific program. An international search is currently under way for the selection of a director, to work under the guidance of the two committees.

Approximately 6 percent of the budget is to be spent on training, particularly at the graduate and postdoctoral levels. The remaining 14 percent of the budget is almost equally divided between basic and applied research. Priority areas have been selected that are compatible with important sectors of the Spanish economy (Table 3). The types of financial support are essentially the same as those described for the CAICYT, including company sponsored projects and joint company-government laboratory projects.

The training part of the program puts its emphasis on graduate and postdoctoral fellows. Given the problems with the Spanish university system, the new curriculums would be developed through close cooperation between universities and government institutes. Four different types of activities are envisioned:

(a) fellowships in government or private research institutes,

(b) postdoctoral fellowships for training abroad,

(c) recruitment of Spanish researchers presently working abroad, and

(d) funding for the creation of new graduate courses.

A comparison of the sums provided by the Mobilization Program and the budgets of the various scientific research agencies would indicate that the Program would more than double the present government outlay for biotechnology. However, it must be noted that the lion's share of that goes for one single project, the Biotechnology Center. It is highly premature to evaluate the achievements of the Program. In its initial phase, it must create the necessary infrastructure for basic research and training, and develop the mechanisms for technology transfer. This is a monumental task, given the long years of neglect under the Franco government. The problems are further compounded by a shortage of experienced scientific administrators and a small pool of young researchers. Clear evidence of this is given by the fact that many top administrators are responsible for a multiplicity of administrative tasks. Nevertheless, one cannot help but be impressed by the intelligence and enthusiasm of the administrative teams, and their creativity and flexibility in trying to get projects under way.

Law on Promotion and Coordination of Scientific and Technical Research: This new law establishes a framework for science and industrial innovation. It establishes a National Plan for Science, and creates an Interministerial Commission of Science and Technology to set it up and implement it. In practice, it provides a legal basis for the present operations of CAICYT and CDTI. Aside from the structural changes, the new Law establishes two important measures. First, it allows government institutes and organizations to create or participate in private companies of a scientific or technological nature. Second, in labor relations, it establishes that the tenure of

Table 3.
PRIORITY RESEARCH AREAS IN THE MOBILIZATION PROGRAM

General Technologies

-Genetic manipulation of microorganisms of industrial significance
-Development of plant and animal tissue culture
-Development of industrial applications of enzymes

Agriculture and Food Processing

-Plant improvement
-Mechanism of nitrogen fixation
-Optimization of fermentation processes
-Improvement of starter cultures
-Bioconversion of lignocellulose
-Biological pesticides

Health Care

-New Antibiotics
-Immunological products and development of diagnostic assays
-Characterization and production of blood proteins
-Production and use of peptides, proteins, and enzymes

Industrial Processes

-Recovery of heavy metals
-Synthesis of organic acids, amino acids
-Bioconversion

Environment

-Sewage and waste treatment
-Heavy metals removal

scientific and technical staff cannot be longer than that of the projects in which they are working. In the case of individuals undergoing training, the contracts cannot exceed 5 years. These measures, overall, promote technology transfer and greater labor flexibility.

International Cooperation: With its accession to the EEC (European Economic Community), Spain can be expected to become a full participant of the EEC biotechnology programs and the Eureka program. Over the years, it has been a member of the European Molecular Biology Organization and the European Molecular Biology Laboratory. It has profited from these agreements mainly in the form of cooperative research and training.

Possibly, the international program with the biggest impact is that administered by the U.S.-Spain Joint Committee on Science and Technology. Its funds come from the agreement for American military bases in Spain. For the present year, it has budgeted $7.6 million. $6.3 million is for 75 applied projects and $833,000 for 44 basic proposals (5). The main areas related to biotechnology are health care and agriculture.

III. UNIVERSITIES AND RESEARCH INSTITUTES

Officially, there are 63 centers of biological research in Spain, of which 24 are in universities, 23 in CSIC institutes and 6 of assorted types (2). It is estimated that there are 1,000 qualified scientific researchers. Most of the important research is conducted in the institutes of the CSIC and the standard-bearer is the Center of Molecular Biology (Centro de Biologia Molecular, CBM). The CBM is the only center that has international recognition and, in large measure, the success of the Mobilization Program depends on the activities of its nucleus of highly competent researchers. (Meetings with CBM staff, as well as experience from earlier visits, provided a base line for comparison with more representative research establishments such as the CSIC's Institute of Biological Research (Instituto de Investigaciones Biologicas, IIB), the National Center of Microbiology, Virology and Immunology (Ministry of Health and Consumer Affairs), and the Technical School for Agronomic Engineers.)

(a) Financial Support: The funding of these research centers involves two different mechanisms. (1) The appropriate Ministries pay the salaries and provide the institutes with operating budgets. (2) In addition, the institutes can apply for grants from the CAICYT. It is evident that institute budgets are insufficient to cover their research expenditures, and grants make for half or more of the total. Even the total expenditures (e.g. $888,000 for the Institute of Biological Research, and $1.2 million for the National Center for Microbiology, Virology and Immunology) (6) are low by U.S. and West European standards. There is ample evidence that the CBM is the best funded of all the institutes while the Technical School has the most serious problems overall since its primary function is teaching. In spite of the low levels of funding, most researchers felt that it ranged from good to adequate.

(b) Scientific research: The overall impression that one gets of Spanish research is that it lags behind that of its European neighbors. Its main

strengths reflect the activities of certain key laboratories in Madrid, Barcelona and Sevilla. Bacterial genetics, applied microbiology, and molecular biology are well established. There has been a traditional interest in intermediary metabolism in mammalian systems, and obvious economic considerations have allowed the establishment of strong groups in plant and animal virology. Developmental biology centered around Drosophila research has also done particularly well.

The CBM has a total staff of 240 (7), and its research activities are very similar to those found in similar institutes in the U.S. or elsewhere in Western Europe. The morale of the staff is high and serious efforts are made to invite foreign scientists to the Center. There are essentially four main areas of activity:

(1) Molecular biology: replication and morphogenesis of phi-29; regulation of protein synthesis in eukaryotes; protein-nucleic acid interactions in ribosomes and chromatin.

(2) Cell biology: brain metabolism; perinatal metabolism.

(3) Animal virology: African swine fever virus, foot and mouth disease, and influenza.

(4) Developmental biology: studies on Drosophila.

The Institute of Biological Research is probably a better indicator of the problems of Spanish research and of how the Mobilization Program can affect it. The facilities we saw were crowded and antiquated even though the equipment seemed modern. Research efforts seemed to be fragmented (ranging from phage genetics to neurobiology) and the size of research groups was small. Here, as elsewhere in Spain, one detects a strong sense of inferiority in relation to the CBM. At the present time, the Institute is being reorganized, the building is undergoing remodeling, and there is discussion of better coordination of research efforts.

The National Center of Microbiology, Virology and Immunology is supposed to be the counterpart of the Center for Disease Control in the U.S. In effect, it is primarily a diagnostic reference laboratory, and it carries out some research on parasitology and virology. Research is, however, a secondary activity that generates supplementary income for the institution.

The Mobilization Program will influence scientific research in two ways: providing additional means of support and in establishing clear-cut priorities. The Biotechnology Center is intended to be an applied R&D institute. Whether it develops as such or becomes a CBM clone will seriously affect the pace of industrial development. A great deal depends on the selection of the Center's Director and the policy directions he will have to follow.

(c) University-Industry Interactions: The most common arrangements involve individual scientists acting as consultants for, or receiving small contracts from private industry. The scientific content of such agreements is

low, and it is primarily seen as a source of supplementary funding. The CBM is the only institute visited that had a significant number of joint projects and contracts with private industry. In addition, CBM researchers maintain good relationships with their industrial counterparts and provide easy access to CBM seminars and conferences.

(d) Staffing: The weakness of Spanish higher education has resulted in a highly uneven quality in the staffs at the research institutes. It is generally accepted that bright, young researchers need to spend a period of research abroad, preferably in the U.S., in order to complete their training. This nucleus of American- and European-trained scientists makes the CBM a successful research institute, and is at the heart of the research groups in the other institutes. Though there are significant numbers of investigators in molecular, cell, and developmental biology, and immunology, they are by no means sufficient to meet the stated needs of the country. In addition, there are severe shortages in the areas of protein chemistry, plant biology, and biochemical engineering. Though no accurate data is available, it is generally known that there is an important pool of Spanish scientists working abroad. One of the objectives of the present government is to attract them back.

(e) Education: At the undergraduate level, the first degree of licenciado in one of the biological departments takes 5 years to complete. The absence of a strict university admission policy, and the outdated nature of the curriculum, results in a large number of poorly trained university graduates. In order to compensate for this, CSIC institutes cooperate with university departments to create graduate curricula that meet some of the multidisciplinary needs of biotechnology. The CBM is a joint institute involving the Autonomous University of Madrid and the CSIC. Such arrangements allow for screening of graduate students and for teaching of advanced courses. Many Spanish scientists are of the opinion that postdoctoral training abroad is almost a necessity for any bright Spanish Ph.D.

IV. INDUSTRY

The two industrial sectors that are likely to be affected by biotechnology are pharmaceuticals and agriculture/food processing. In both sectors, large foreign multinationals and small to medium-sized Spanish companies compete for the market. No significant biotechnology activities exist in the agro-food sector, so I have concentrated on Spanish pharmaceutical firms (by Spanish standards: one large, two medium-sized) and two small start-up firms working on diagnostics. The characteristics of these companies are summarized in Table 4. Though not actually visited, Biokit is considered one of the most innovative Spanish biotechnology firms.

ANITBIOTICOS, S.A.: With annual sales of $141 million, Antibioticos is the largest pharmaceutical company in Spain, with 50 percent of its production being exported (8). Its main product line is represented by antibiotic intermediates and it is the world's third largest producer of beta-lactams. Its production facility is in Leon, along with most of its R&D. There is a basic research unit in Madrid, which has groups working on the secondary

Table 4.
CHARACTERISTICS OF COMPANIES VISITED

	Antibioticos, S.A.[1]	Laboratorios Abello[2]	Instituto Llorente[3]	Invesgen[4]	Ingenasa[5]
Annual Sales (in Ptas)*	24bn ($141M)	5bn ($29M)	5bn ($29M)	200M ($1.2M)	660M ($3.9M)
Employees	1850	200		40	15
Products	Antibiotics intermediates	Over-the-counter products Vitamin C	Vaccines Antibodies Blood products	Markets products of Diagnostic Pasteur, Achem, & Quidel	Contract R&D
Research Areas	New antibodies Immobilized enzymes Interferon IL-2	Chemical synthesis Pharmacology	Monoclonal antibodies to hormones Sexually transmitted diseases Blood groups Hepatitis	Monoclonal antibodies for diagnostics	Animal vaccines Diagnostics for animal health care Possibly plant genetic engineering
Corporate Affiliation	---	Merck, Sharp & Dohme	Rocador Groups	INDUYCO Group	Explosivos Rio Tinto

*1985 average exchange rate: $1 = Ptas 170.04. M = millions, bn = billions
1.Perez-Aranda, Augustin, Director of Research, Antibioticos, S.A., personal communication, March 19, 1986.
2.Gomez-Parra, Vicente, Research Director, Abello, S.A., personal communication, March 18, 1986.
3.Sempere, Rafael Llopis, Scientific Director, Instituto Llorente, personal communication, March 19, 1986.
4.Herranz Lopez, Eugenio, Planning Director, Invesgen, personal communication, March 18, 1986.
5.Molina, Alejandro Herrero, Director General, INGENASA, personal communication, March 21, 1986.

metabolism of filamentous fungi, development of vectors, screening and application of recombinant DNA methods for new antibiotics, and use of immobilized enzymes. All of this work is directly related to the improvement of antibiotic production. In collaboration with the CBM, they cloned and produced interleukin-2 and interferon, but a commercial analysis resulted in the projects being dropped. Nevertheless, it is felt that the company gained by the introduction of a series of new techniques.

Antibioticos originally had four owners, but one of them, Mr. Abello (see Laboratorios Abello) bought out the other three owners, and is presently reorganizing it with expansion of the R&D department.

LABORATORIOS ABELLO: This company was originally government-owned, and then was acquired by Mr. Abello. The company was purchased by Merck, Sharp & Dohme in 1983 and the R&D laboratory was reorganized. The section that worked on allergy and related diseases remained independent and developed its monoclonal antibody technology. The major part (still named Laboratorios Abello) continued producing and selling its traditional products which are primarily over-the-counter remedies such as Frenedol, an anti-flu formulation, and Prevolone, a vitamin complement. Most of these products are for the Spanish and third world markets. The research laboratory was assigned the task of doing chemical synthesis, screening drugs, and running pharmacological studies. The laboratories themselves were modern and well equipped, but appeared to be underused.

The staff of the company is still puzzled as to what their role is in the Merck organization. It is certainly felt that this acquisition by a foreign multinational has not led to the introduction of new technology nor to the development of new products for the Spanish market. Since multinationals most often maintain their R&D activities in their home countries, this often results in a reduction in their R&D activities in Spain and leads to a general feeling of job insecurity in the acquired firms.

INSTITUTO LLORENTE: This is an old company with a good reputation for blood products and vaccines. Several years ago, it decided to move into biotechnology. This was encouraged by contacts with the CBM and stimulated by the programs of CDTI. Not only has the Instituto developed monoclonal antibodies, but it has now developed mouse monoclonals for use in Rh blood tests. Monoclonal antibodies are also being used for human pregnancy tests, hormone purification and for treatment against parasites. The company has received CDTI funding for development of tests for sexually transmitted diseases [Ptas 163 million ($959,000) for 3 years] (9). Newly remodeled laboratories are well designed and equipped.

This company was recently bought out by Laboratorios Fides, a medium-sized Catalan pharmaceutical company, which is part of the Rocador Industrial group. It is felt that the introduction of new biotechnology products will take some time because some of the technology (particularly at the production end) is not readily available in Spain. There is also the uncertainty of whether the owners and managers of Spanish industrial groups are willing to accept the lack of short-term profits from new biotechnology products.

INVESGEN: This is a small biotechnology start-up company with a self-conscious emphasis on confidentiality. It markets products from Diagnostics Pasteur, Achem and Quidel, which provide a significant part of its present revenues. Their business strategy is based on having this cash flow until they can develop their own processes and products. Its basic technologies are monoclonal antibodies and tissue culture, and its first products are likely to be diagnostic kits for human use. In order to maintain industrial secrecy, they have chosen not to accept any government support. INVESGEN is part of the large INDUYCO industrial group which owns the department store chain, El Corte Ingles, one of the most profitable in Spain. INVESGEN has just completed remodeling of new laboratory facilities in Madrid which are up to modern standards.

INGENASA: This new start-up company began in 1981 and was a joint venture between the state-run National Industrial Institute (INI) and a private company. The initial government contribution of Ptas 55 million ($323,000) (10) was for a coordinated project with the CBM for research on the swine fever virus. The objective of the project was to develop a diagnostic assay and then a vaccine. In 1983, the government decided to privatize the companies in which it had invested and INGENASA was acquired by Explosivos Rio Tinto (ERT), a large industrial group that includes pharmaceuticals. ERT has total annual sales of Ptas 280 billion ($1.52 billion), while the pharmaceutical business accounted for Ptas 5 billion ($29.4 million) (10). INGENASA is now entering a new and uncertain phase as a contract R&D company, providing expertise in genetic engineering, tissue culture and plant cell fusion to ERT. In those areas where there is no direct conflict with ERT, it can enter into contracts with other companies. However, the limited size of its operations makes that unlikely unless ERT increases the size of its investment. The exact role and scale of operations of INGENASA within the ERT group is still very unclear and remains to be decided by the corporate management of ERT.

BIOKIT: Biokit was established by the Rubiralta family for the purpose of using monoclonal antibody technology in the production of diagnostic kits. It has moved aggressively to market tests for: (1) infectious diseases (streptococci), (2) chronic conditions (rheumatoid arthritis, C-reactive protein, toxoplasma), and (3) sexually transmitted diseases (syphilis).

Biokit has grown rapidly to a staff of 120, with sales of Ptas 500 million ($2.8 million), and a net profit of Ptas 80 million ($450,000) (11). Approximately 80 percent of their sales are exported with Japan and the U.S. as important markets. In order to rapidly acquire new methods and processes, it has pioneered in the concept of the flying laboratory (i.e., sending scientists for short periods of time to first-class labs such as CDC, Harvard). Biokit is also the first Spanish biotechnology company to participate in a Eureka-sponsored project. This is in collaboration with PA Technology of the U.K., for the development of diagnostic kits for sexually transmitted diseases.

INDUSTRIAL OVERVIEW

The entry of Spain into the EEC will have a profound effect on its industry and its institutions. Spain will change from a frequently ignored, protected market to a growing market for high technology products with open access to the EEC. In biotechnology related industries, only the human health sector is applying the new technologies, with the multinationals continuing to do the bulk of their R&D outside of Spain. Potentially, the applications in agro-food could be very important, but research is just beginning. It still remains to be seen whether the agro-food industry will be responsive to the new developments. Of the companies visited, only Antibioticos and Biokit have a vigorous export trade, with all of the others focusing on the domestic market, and to a lesser degree, on the Latin American market. Aside from antibiotics, the new biotechnology products will be in human and animal diagnostic kits and vaccines.

Up to now, industrial development of biotechnology has been dependent on the scientific expertise of the CBM and on the new policies of the government. The CBM has been instrumental in introducing new technologies to the companies, and in some cases has spun-off projects to be commercialized. Nevertheless, the scientists of the CBM see their primary mission as basic research and would prefer to limit their involvement in industrial projects. Technology transfer will become the responsibility of the new Biotechnology Center, which represents the single largest investment of the Spanish government in biotechnology.

The use of biotechnology in Spanish industry is limited by the availability of trained scientists and managers (in particular those experienced in developing and marketing new products). In almost all cases, key staff members have spent a significant period of time working in the U.S. At a higher level, the understanding of the new technologies and their commercial implications is fairly unsophisticated among industrialists and financiers. The phenomenon of three new small companies (INVESGEN, INGENASA and Biokit), and a totally new operation in an old, established one (Instituto Llorente) are remarkable when viewed against this background. As earlier remarked, all of these firms are part of larger industrial groups which may only be using the new technologies as a public relations ploy or they may actually be willing to invest the necessary money and time to develop new products and processes.

V. CONCLUSION

At first glance, Spain seems to offer little in the way of biotechnology. It lacks well established research laboratories such as those in France and the U.K., and it does not have large multinational pharmaceutical and chemical firms such as Italy. Information on Spain is scant and not very positive. An actual visit to Spain provides a different perspective. There are two major factors at play: one is a pool of good biological scientists with a strong nucleus at the CBM; the other is the political will to develop biotechnology in Spanish industries. The community of scientists in research institutes and companies and the cadre of new

government administrators seem to interact well and have created an exciting and rapidly changing environment for technological innovation.

This is not to say that Spain does not face daunting obstacles. Some of these are amenable to purely Spanish solutions. Among these are a necessary expansion and improvement of the scientific base in the biological sciences. The Mobilization Program is an important step in that direction, but once again it must be emphasized that the majority of the funds are committed to the Biotechnology Center. If successful, this Center will increase the critical mass of biological scientists and provide an institution for technological transfer. Depending on the level of scientific activity, this could make Madrid a much more important international center than it has been up to now. Experience in the U.S. and Europe would indicate that these goals are more often achieved by a decentralized system, with the introduction of new research and techniques into the various regions of the country. An increase in professional opportunities would attract back many of the successful Spanish scientists currently working in the U.S. University and graduate reforms are necessary to bring training up to international standards. It is also important to acquire new customers for the new technologies, and it is questionable whether there is a large enough Spanish industrial base that can use them or whether the industrialists have the necessary sophistication to develop the necessary long-term strategies.

In entering the highly competitive world market for new biotechnology products, it is unlikely that Spain can go it alone. It needs to acquire the new technologies and management skills very rapidly in order to catch up. In manufacturing, it has done this, attracting multinationals (e.g., Ford's automobile production facility in Valencia). More recently, it has followed the same strategy in high technology: AT&T is building a $210 million microchip production facility near Madrid and Corning Glass is investing $30 million in an optical fiber plant (12). This same approach could be applied to biotechnology except that some of the most attractive U.S. partners would be small to medium-sized companies without the resources of an AT&T or a Corning. However, whether U.S. companies, large or small, choose to establish themselves in Spain will depend on Spanish government policies concerning patent protection and drug pricing. Entry into the EEC has had a favorable effect on Spanish patent law, which will conform to EEC standards by 1992. In the interim, the burden of proof has been shifted to the manufacturer who lays claim to a new process for a drug already protected by a patent. It is also likely that Spanish prices will rise to approach EEC levels. It is the response of the industrial sector that will determine the ultimate success of the Moblilization Program and biotechnology in Spain.

ACKNOWLEDGMENTS

Jose Luis Lopez, Commercial Specialist, Foreign Commercial Service, American Embassy, Madrid

John D. Perkins, Commercial Counselor, Foreign Commercial Service, American Embassy, Madrid

Leroy Simpkins, Science Attache, Scientific & Technological Affairs, American Embassy, Madrid

Diana Valderrama, Science Officer, Scientific & Technological Affairs, American Embassy, Madrid

REFERENCES

1. Economic Trends Report: Spain, U.S. Department of State, January 1986.

2. Programa Movilizador de Biotechnologia, Ministerio de Educacion y Ciencia, June 1985.

3. Sebastian, Jesus, Vice President, CSIC, personal communication, March 21, 1986.

4. CDTI, Annual Report, 1984.

5. U.S.-Spain Science and Technology Cooperation, Report on 13th U.S.-Spain Joint Committee Meeting on Science and Technology in Madrid, March 25, 1986.

6. Morrondo, Rafael Najera, Director, National Center for Microbiology, Virology and Immunology, personal communication, March 24, 1986.

7. Spanish Genetic Engineering and Biotechnology Center, CSIC.

8. Perez-Aranda, Augustin, Director of Research, Antibioticos, S.A., personal communication, March 19, 1986.

9. Sempere, Rafael Llopis, Scientific Director, Instituto Llorente, personal communication, March 19, 1986.

10. Molina, Alejandro Herrero, Director General, INGENASA, personal communication, March 21, 1986.

11. Manent, J., Manager Director, BIOKIT, S.A., personal communication, July 1986.

12. Financial Times, London, June 16, 1986.

APPENDIX

Organizations and Individuals Visited

Government

Department of Scientific Policy, Ministry of Education and Science: Dr. Emilio Munoz, Director; Dr. Armando Albert, Scientific Adviser.

High Council for Scientific Research (CSIC): Dr. Jesus Sebastian, Vice President.

Center for Technological and Industrial Development (CDTI): Mr. Jaime Vallori Bennasar, Director; Dr. Regina Revilla, Assistant Director for Biotechnology.

Research Organizations

Technical School for Agronomic Engineers, Polytechnic University of Madrid: Dr. Maunel Arroyo, Director: Dr. Jose Luis Sainz Velez, Secretary.

Center of Molecular Biology, Autonomous University of Madrid: Dr. Pedro Ripoll, Director; Dr. Luis Enjuanes, Group Leader (also Executive Secretary of the Board of the new Biotechnology Center).

Center of Biological Research: Dr. Manuel Ramirez de Verger Lobo, Director.

National Center of Microbiology, Virology and Immunology: Dr. Rafael Najera Morrondo, Director.

Industry

Laboratorios Abello: Dr. Vincente Gomez Parra, Director of Research.

Antibioticos, S.A.: Dr. Agustin Perez Aranda, Head of Research Department; Dr. Victor Rubio, Group Leader.

Instituto Llorente: Dr. Rafael Llopis Sempere, Scientific Director.

INVESGEN: Dr. Eugenio Herranz Lopez, Director of Planning; Dr. Jose R. Pellon Olagorta, Assistant Director.

INGENASA: Dr. Alejandro Herrero Molina, Director General.

SECTION G

BIOTECHNOLOGY IN SWEDEN

SUMMARY

Sweden plays an important role in biotechnology among the smaller countries in Europe. The key government organization involved in the promotion of biotechnology is the Swedish National Board for Technical Development, which funds projects of industrial importance. In addition, the government has drafted a proposal for a National Program in Biotechnology. The industrial sector has a number of important medium-sized, multinational companies which have established profitable niches in the manufacture of laboratory equipment, biochemical reagents, and fermentation/downstream processing equipment for the research, pharmaceutical, and food processing markets.

I. INTRODUCTION

Sweden is the most advanced of the Nordic countries, combining a highly industrialized economy with a well developed welfare system. Though its economy had performed poorly in the 1970's, the devaluation of the krona in 1980, and again in 1982, led to an export boom in 1983 and 1984. Indications were that the economy was slowing down in 1986. The decrease, however, in the price of oil, and in the value of the dollar, has led to a more optimistic outlook with a predicted growth rate of 2 percent, an inflation rate of 3-4 percent, and a trade surplus of SKr 28 billion ($3.25 billion)*. It is expected that the government deficit will be less than 5 percent, while unemployment will remain around 2.7 percent. There is concern about wage increases, which will probably be 6-7 percent in the private sector, and pressures in the public sector that could lead to labor unrest (1).

The Swedish economy depends on exports, with 50 percent of its products being sold abroad. The U.S. is presently the single largest market, accounting for 11.6 percent of exports, while Europe as a whole accounts for 70 percent of exports. Most exports are in engineering products, pharmaceuticals, steel, and paper products. Imports are in capital goods, oil, manufacturing equipment, and computers. The Swedish government has taken a major role in restructuring industry by transforming depressed sectors (e.g., shipbuilding), into profitable growth sectors (e.g., transportation) (1).

Sweden has a well developed range of biotechnology activities, particularly in the industrial sector. In order to study the various aspects of Swedish biotechnology, 14 meetings were held with representatives of various organizations involved in biotechnology.

*Average exchange rate for 1985: Swedish krona (SKr) 8.6039 = $1.

II. GOVERNMENT POLICY

Sweden has the best developed scientific infrastructure of any of the Scandinavian countries, which compares well with many of its European neighbors. Swedish expenditures for research and development (R&D) in 1985 totalled more than SKr 19 billion ($2.21 billion), of which SKr 10 billion ($1.16 billion) were spent by the government. Funding of R&D is, therefore, approximately equally shared by the government and Swedish industry. This expenditure is equal to 2.5 percent of GNP, making Sweden one of the leaders in R&D spending in the OECD.

Government funding of R&D is through three different mechanisms: (1) allocations to universities, (2) grants from the research councils, and (3) grants from specialized agencies, such as the Swedish National Board for Technical Development (STU), and the National Food Administration. The first two mechanisms are directed towards basic research, while the third is concentrated on applied research. The Swedish Research Advisory Board has the responsibility of coordinating the activities of the scientific community with the missions of the government agencies.

The principal organizations involved in support of biotechnology are the Natural Sciences Research Council, the Medical Research Council, the Swedish National Board for Technical Development (STU), and the Swedish Industrial Board (SND). In 1985, total government expenditures on biotechnology were estimated at SKr 175 million ($20.3 million), while industry expenditures were approximately SKr 650 million ($75.5 million).

In March 1984 the Swedish government presented a comprehensive program for R&D in the public sector. The 1984 Research Policy Bill (2) was designed to address a number of problems in government R&D funding. These were identified as:

- o finding an appropriate balance between the resources allocated to specialized government agencies and to the universities and research councils,
- o maintaining uniform scientific quality in all project areas,
- o simplifying the administrative procedures involved in applying for and distributing grants,
- o promoting university-industry interactions, and
- o defining scientific priorities.

The bill included the following measures:

(1) It exempted research and research training from spending cuts, and actually increased government spending by SKr 150 million ($17.4 million) in 1985.

(2) It allocated an additional SKr 125 million ($14.5 million) for basic research under the Ministries of Education and Agriculture. This provided more resources to the research councils, particularly in the areas of science and technology, and provided 170 new research appointments at intermediate levels. It also allowed for the purchase of capital equipment and scientific exchanges with foreign countries, and emphasized basic research in the activities of the various government agencies. Fellowships for Ph.D. students were lengthened from four to six years.

(3) University-industry activities were promoted. A review to find more effective mechanisms for the promotion of these activities was commissioned.

(4) More grants for Swedish researchers abroad were made available, while tax exemptions would be provided to visiting foreign scientists in Sweden. Additional resources were allocated for Swedish scientific attaches abroad.

(5) The bill emphasized four priority areas: environmental research, information technology, materials research, and biotechnology.

(6) A new, 3-year program (1984-87), worth SKr 2.2 billion ($255.7 million), was approved for the STU.

The Swedish National Board for Technical Development (STU) is part of the Ministry of Industry. It has responsibility for furthering basic research and technology transfer for the development of new products and processes, and is generally acknowledged as the single most influential government agency involved in biotechnology (3). In 1985, its budget was SKr 700 million ($81.4 million). The STU's Medical, Welfare and Life Sciences Department is responsible for biotechnology, and it spent SKr 30 million ($3.49 million) in 1985. This sum is equivalent to that spent by the Medical Research Council. The STU supports both basic and applied research at the universities. Its first major basic research program was in genetic engineering (which has been running for 8 years) and this has helped increase the number of Swedish laboratories applying this new technology. Programs in separation technology and carbohydrate chemistry have also been established. In the industrial sector, the STU makes a point of assisting small and medium-sized companies, lending up to 50 percent of the cost of applied projects. If the project fails for either technical or commercial reasons, the loan is written off (3).

A National Committee for Biotechnology has been established, for which the STU will act as the administrative arm. The Committee has proposed a National Program for Biotechnology and requested an annual budget of SKr 35 million ($4.08 million) (3).

The Swedish National Industrial Board is also part of the Ministry of Industry, and is responsible for promoting industrial innovation in small and medium-sized companies. Since the Board does not have funds of its own, it provides consulting services in finance, management, marketing, and technology transfer. The Board also analyzes the potential impact of new government

regulations on industry. One program that has been useful, is a tax relief fund that enables companies to pay their taxes into an escrow account, from which they can borrow for purposes of capital investment and expansion into overseas markets. It cannot, however, be applied towards new technology. The Board also assists companies in obtaining assistance from the Industrial Fund (4).

The Industrial Fund is a venture capital fund created by the government in order to promote high technology industries. The Fund provides up to 50 percent of project costs (which has to be between SKr 5 million and SKr 50 million) as a loan or a subsidy. The interest rate on these loans is 4 percent above the discount rate. In the event that the project fails, the loan is written off. These loans are considered expensive by industry and are used for projects that are too risky for commercial banks (4,5).

III. UNIVERSITIES AND RESEARCH INSTITUTES

Sweden has a number of university laboratories doing quality research in the biological sciences. Among these are: Lund, Umea, Uppsala, the Royal Institute of Technology, and the Karolinska Institute. Of particular importance, in relation to technology transfer, are the Departments of Biochemistry and Biotechnology at the Royal Institute of Technology in Stockholm, and the Department of Biochemistry at the University of Uppsala. [Scheduling difficulties only allowed a visit to the Royal Institute of Technology, though there were discussions with members of the faculty of the University of Lund.]

The Royal Institute of Technology is considered one of the main academic centers of biotechnology research, with an important segment located in the Departments of Biochemistry and Biotechnology. The Department of Biotechnology has an annual budget of SKr 4 million ($465,000), 20 percent of which comes from the university, 20 percent from industry, and 60 percent from government grants. The Department of Biochemistry has a budget of about SKr 6 million ($697,000), and is part of the School of Chemical Engineering, with a staff of 35. It conducts research in six major areas: microbial metabolism, rDNA technology, bio-organic synthesis, plant tissue culture, fermentation technology, and extraction of extracellular enzymes. Principal research projects appear in Table 1. The Department collaborates with KabiGen on the protein A fusion project, and is setting up a pilot plant facility with equipment donated by Alfa-Laval and Pharmacia (6).

The Biochemistry Department also has a 4-year program, leading to a degree in chemical engineering, specializing in biotechnology (the last year is spent in biology courses, including a 3-month project). This program has a full complement of 25 students.

At the University of Lund, the Institute of Technology represents a focus for biotechnology. Its principal research areas are indicated in Table 1. Some of the projects are similar to those at the Royal Institute of Technology, but there is also work on enzymes and immunological systems (7).

Table 1.
Selected Research Laboratories

	Department of Biochemistry and Biotechnology Royal Institute of Technology	Lund Institute of Technology University of Lund
Principal Research Projects	I. Microbial Metabolism Metabolic pathways in solvent producing Clostridia Continuous cultivation of yeasts in phenol chemostat Metabolism of Mycotoxins II.Recombinant DNA Gene fusion vectors with staph protein A Protein secretion in Bacillus & Staphylococcus Cloning systems in Streptomyces III.Biorganic synthesis IV.Plant Tissue Culture Function & degradation of fungicides Secondary metabolites from plant tissue culture V. Fermentation Technology Development of sensors & computer systems for control Adsorbed cells for metabolite production Scale-up of rDNA processes VI.Separation Technology Large-scale, two-phase partition Affinity extraction of proteins	I. Enzyme Technology Affinity processes Design of biosensors Immobilized restriction enzymes and ligases II.Cell Culture Plant cells - alkaloids, drugs Animal cells - interferon, monoclonal antibodies Bacteria - Steroids, vitamins, interferon Yeasts - Ethanol Fungi - Antibiotics III.Immunology Production of antibodies & use in immunotherapy IV.Fermentation & Downstream processing Purification techniques

In addition to the two institutions described above, there are strong groups in nucleic acid biochemistry at the University of Umea, in separation and purification technology at the University of Uppsala, and in cell biology, virology, and immunology at the the Karolinska Institute.

University-Industry Interactions: Technology transfer from university laboratories to industry is considered one of the strengths of Swedish biotechnology. The University of Lund has established the Ideon Science Park, which includes a number of biotechnology firms. Pharmacia has always had close ties to the Biochemistry Department at the University of Uppsala. The county of Stockholm has committed SKr 60 million ($6.97 million) for the establishment of the Huddinge Center for Biotechnology, adjacent to the Karolinska Institute (8,9). This will be a combined basic research/technology transfer institute which, it is hoped, will attract industrial projects.

An important organization in promoting industrial biotechnology is the Biotechnology Research Foundation (BRF), an association of 50 Scandinavian companies. BRF's mission is to promote biotechnology research, foster communication between scientists and the member companies, and develop educational programs. Given the efforts of national biotechnology programs and EEC activities, the BRF hopes to increase collaboration within the Nordic bloc. Its principal activities are (10):

- Research: BRF and STU provide an annual budget of SKr 2 million ($232,500) for grants to individuals and groups doing research in selected topics.

- Information exchange: BRF sponsors symposia, conferences, and courses.

During the initial period, 1982-85, the BRF supported research in four areas: heterogeneous fermentation systems, stabilization of immobilized cell systems, membrane technology, and regeneration of co-enzymes. In addition, there were two investigator-initiated projects: plant improvement and rDNA techniques, and molecular cloning of cellulase genes (11).

For the period of 1985-88, three research areas have been selected: prevention of contamination by microorganisms during production, control of by-product formation during fermentation, and stability of microorganisms under production conditions. The BRF has also set up a new program in yeast molecular biology at a cost of SKr 2.5 million ($290,600) over a 4-year period. In international terms, BRF's research funds are small, but it serves a useful function in sensitizing Scandinavian companies to the scientific and industrial potential of biotechnology.

IV. INDUSTRY

Swedish industry has a number of important companies with well established biotechnology activities. A long tradition in engineering, production equipment, and expertise in protein chemistry and separation techniques has resulted in the following industrial profile (12):

(1) Pharmaceutical companies: medium-sized firms such as Astra, Leo, and KabiVitrum.

(2) Companies specializing in laboratory, fermentation, separation, and downstream processing equipment and technologies: Alfa-Laval, LKB, and Pharmacia.

(3) Provendor Group (part of the Volvo industrial combine).

(4) New biotechnology companies such as BioCarb and KabiGen.

The rapid growth of Fermenta, the takeovers (or attempted takeovers) of various companies, the establishment of venture capital funds, and of new biotechnology companies, have made the industrial scene a volatile one. The small size of Sweden, and its limited resources, have led to the expectation that there will be a shakeout in this industrial sector, with the Volvo industrial group playing a major role.

Pharmaceutical Companies

ASTRA is the largest of the Swedish pharmaceutical companies, but is considered fairly small on a global scale (see Table 2) (13). It has done very well, recently, with the introduction of a new anti-asthma drug, but its principal sales are in the area of cardiovascular and local anesthetic drugs (14).

KABIVITRUM is a state-owned pharmaceutical company, which has specialized in the purification of drugs from natural sources (see Table 2) (15). The most important of these is human growth hormone (hGH), which accounted for 60 percent of its profits in 1985. During the past year, however, KabiVitrum has had to remove hGH and Factor IX from the market because of potential contamination by Creuzfeldt-Jakob prions and AIDS virus, respectively. This has resulted in a sharp decline in earnings. KabiVitrum is now producing genetically engineered hGH, developed in collaboration with Genentech of the U.S., and is trying to find a new procedure for the isolation of tissue plasminogen activator (TPA) from fibroblast cultures. It has also started marketing Fragmin, an anticoagulant, which is a fragment of heparin. KabiVitrum is relatively small, but is considered to have good production technology and to have been successful at introducing recombinant DNA (rDNA) technology into its laboratories. It has, therefore, been a major target for acquisition, initially by Fermenta, and more recently by Astra (16). If Astra were successful, this would lead to an important consolidation of the Swedish pharmaceutical industry.

Equipment and Separation Technologies

ALFA-LAVAL is a large, multinational engineering group that had its start in the manufacture of equipment for the dairy industry. About 88 percent of its sales are outside of Sweden, with its principal markets being France, West Germany, the U.S., and the U.K. (16). Of its 10 business divisions (see Table 3), Animal Health and Nutrition, Separation, and Technology are involved in biotechnology. Recognizing the increasing importance of biotechnology,

Table 2

Selected Swedish Pharmaceutical Companies

	Astra	KabiVitrum
1985 Sales in SKr (% change from previous year)	4.463bn ($518.7M)* (+13%)	1.377bn ($160.1M) (+12%)
Profits in SKr (% change from previous year)	1.041bn ($120.9M) (+26%)	117M ($13.6M) (-55%)
Principal Products	Cardiovascular agents Local anesthetics Respiratory agents Anti-ulcer drugs	Genetically engineered human growth hormone Fragmin (anti-coagulant) Heparin Factor IX
R&D Projects	N/A	Anti-thrombin III TPA

*Average exchange rate for 1985: SKr 8.6039 = $1.
bn = billions, M = millions

Table 3.
Laboratory, Separation & Production Equipment Companies

	Alfa-Laval	LKB	Pharmacia
1985 Sales in SKr (% change from previous year)	10.046bn ($1.17bn)* (+13.5%)	996.4M ($115.8M) (+21.9%)	3.398bn ($394.9M) (+19%)
Profits in SKr (% change from previous year)	651M ($75.7M) (+56%)	32.3M ($3.75M) (+19.2%)	741M ($86.1M) (+16%)
Business Sectors (% of total sales)	Food Engineering (29.3%) Agriculture (21.5%) Marine & Power (12%) Biotechnology (1.9%) Animal Health & Nutrition (3.8%) Thermal (7.5%) Separation (5.6%) Dosing & Analyzing (4%) Technology (0.6%) Finance	Research & Industrial Group: Chromatography (33%) Electrophoresis (16%) Biotechnology Spectrophotometry & Protein Analysis (8%) Clinical Systems Group: Diagnostics Systems (13%) Analytical Instruments (12%) Microtomy Systems Clinical Microbiology (9%)	Biotechnology (25%) Health Care (24%) Ophthalmics (23%) Diagnostics (21%) Other (7%)
R&D Budget (% of sales)	381M ($44.3M) (3.8%)	79M ($9.2M) (7.9%)	470M ($54.6M) (13.8%)
Areas of R&D	Separation techniques Prevention of mastitis in cows Process Engineering	Large Scale Separation Equipment Affinity Chromatography material	Derivatives of Salazopyrin New applications for Healon Non-isotopic diagnostic assays Cancer diagnostics Large scale separation methods
Joint Ventures (Biotechnology) with U.S. Firms	2.6% equity in Genentech $1M in equipment & $2.5M in research contract with MIT		See Table 4.

M = millions, bn = billions
*Average exchange rate for 1985: SKr 8.6039 = $1.

Alfa-Laval has created a new business area, Biotechnology, which had invoiced sales of SKr 190 million ($22.1 million) in 1985, and is centered around the Swiss company, Chemap (the world's largest manufacturer of fermenters), acquired by Alfa-Laval in 1985 (17). This allows Alfa-Laval to provide a broad range of manufacturing equipment, including fermenters and downstream processing systems (18). Alfa-Laval also hopes to use its expertise to produce equipment for research laboratories. It has recently announced the formation of a joint venture with Pharmacia and Biolink to develop new technologies in separation and purification of biological products.

The Animal Health and Nutrition Division has been collaborating with BioCarb to find a method for preventing mastitis in dairy cows. It is also doing research on the replacement of antibiotics in animal feed. The Technology Division is responsible for the new Biotech Center, which consists of a highly flexible pilot plant and its scientific and engineering staff. This allows companies to develop industrial processes of volumes ranging from 100 to 1,000 liters. Alfa-Laval has also increased its research capabilities in this sector by entering into an agreement with the Department of Biochemical Engineering at the Massachusetts Institute of Technology (MIT) for research in process technology. Alfa-Laval will provide $1 million worth of equipment, as well as a $2.5 million research contract. Alfa-Laval also owns 2.6 percent of the equity in the U.S. company, Genentech (18).

LKB is one of the major manufacturers of laboratory equipment for biological research (e.g., it has one-third of the market for electrophoresis equipment and is the market leader in low-pressure liquid chromatography equipment). About 41 percent of its sales are in Western Europe, and 27 percent in North America. Its business has been growing rapidly, at a rate of 7 percent annually, and is organized into two groups: Research and Industrial, and Clinical Systems (see Table 3) (19).

LKB has decided to apply its expertise in laboratory systems to the development of large-scale, downstream processing systems, and has created a new Biotechnology Division. This division collaborates with client companies to develop new processes using experimental equipment and techniques that can then be modified for industrial production.

There are three major areas of biotechnology R&D at LKB: (1) the application of HPLC to large-scale purification of biological products, particularly proteins, (2) the development of primary separation techniques to reduce the volume and heterogeneity of crude homogenates, and (3) development of assays using antibodies labeled with flourescent groups which have the same sensitivity as isotope-labeled ones, but without the attendant health hazards (20).

In the past, LKB, Pharmacia, and Alfa-Laval have concentrated on their individual markets. It is clear that, now, they are entering into active competition. LKB is going into downstream processing and Alfa-Laval is becoming involved in the manufacture of laboratory equipment.

PHARMACIA is one of the largest pharmaceutical companies in Sweden, though rather unusual in that its expertise is in bead technology and high molecular

weight compounds such as dextran and hyaluronic acid. In reality, Pharmacia is a specialist firm in human health care and separation technology. About 98 percent of sales are outside of Sweden, with 40 percent in the U.S., its single largest market.

Pharmacia is organized into four business sectors, three of which deal directly with human health care (see Table 3) (21). The strategy in human health care is to find specialized niches in which they can apply their technologies. In the biotechnology sector, Pharmacia intends to become a major supplier of reagents and systems to both research laboratories and industrial facilities.

In the Health Care Sector, there are several important product areas. Salazopyrin, an old drug used in the treatment of colitis, is now being applied in the therapy of rheumatoid arthritis. As the population in Western countries ages, there is an increased need for wound treatment, and Delorisan has been introduced as a cleansing agent for wounds. Drug delivery is an important element in both analgesic and chemotherapy treatments, and the "Port-a Cath" system (a portable pump system) is being marketed for use both in hospitals and in the home. Dextran is still being used as a plasma replacement. R&D in this sector has focused on finding derivatives of Salazopyrin, and new clinical uses for dextran.

In the Ophthalmic Sector, the objective is to provide a total system to the ophthalmic surgeon. Pharmacia is a major manufacturer of intraocular lenses, and of Healon, an hyaluronic acid compound, used to replace ocular fluid during lens implantation. R&D in this sector involves finding new clinical applications for Healon, as well as the design and manufacture of new types of lenses.

The Diagnostics Sector is concentrating on developing in vitro assays for allergies. One of its principal products is the RIA-based RAST kit that allows identification of 200 allergens. Pharmacia also produces test kits for bacterial strains, such as streptococci and gonococci. R&D efforts are directed towards replacing the present tests with non-isotopic ones, and developing diagnostic tests for specific types of cancers.

The Biotechnology Sector has been the fastest growing (sales up by 27 percent in 1985), with 98 percent of it products being sold abroad (40 percent of that in the U.S.). This sector is composed of three divisions: Laboratory Separations, Molecular Biology, and Process Separations. Laboratory Separations produces equipment, systems, and media for centrifugation, chromatography, and electrophoresis. It has recently introduced the FPLC system as an alternative to the HPLC systems sold by many of its competitors. This system of liquid chromatography combines speed with media and solutions that do not inactivate biologically active proteins. R&D in this division is directed towards development of new separation materials for specific applications. The Molecular Biology Division includes Pharmacia P-L Biochemicals in the U.S., and is responsible for special reagents such as enzymes, oligonucleotides, and plasmid vectors. It has recently introduced a DNA synthesizer, the first to be manufactured in Europe, and the FAST system for gel electrophoresis of proteins. R&D in this division is directed towards

production of new reagents and equipment. The Process Separation Division produces the media, equipment, and systems for large-scale purification of biological materials.

The Biotechnology Sector is also responsible for three new biotechnology companies: BioCell, BioNova, and Biosensor. BioCell was recently integrated into this sector, and is responsible for developing new techniques for the production of active polypeptides. This includes growth of animal cells on beads and in suspension, application of rDNA methods, and production of polyclonal antibodies. BioNova is a 50:50 joint venture with the STU, and has 50 scientists in the Wallenburg Laboratory, at the University of Uppsala, working on rDNA methods.

Some specialists in biotechnology have expressed the view that Pharmacia has followed a conservative policy of modifying and developing those technologies already available in-house, while adapting slowly to the new rDNA and monoclonal antibody technologies. Continuation of such a policy would have made Pharmacia increasingly vulnerable to international competition. It is now evident that Pharmacia intends to follow a much more aggressive policy, with a strong commitment to R&D (almost 14 percent of sales), as well as a series of acquisitions and agreements (see Table 4) that will strengthen its present capabilities and provide access to new technologies. The creation of BioLink, with Alfa-Laval, provides an opportunity to enter the market for comprehensive biotechnology production facilities. Plans are to have a work force of 200, with access to the technology of Chemap. Current projections are that sales will reach SKr 500 million ($58.1 million) within 2 years. BioLink's financial situation is strengthened by Volvo becoming its largest stockholder, and by trading shares on the OTC market in the U.S. Current plans are for shares to be traded on the Tokyo market as of next year.

The VOLVO INDUSTRIAL GROUP is the largest industrial group in Scandinavia, with annual sales of SKr 86,196 million ($10 billion) in 1985, and profits of SKr 4.48 billion ($520.7 million) (22). Volvo experienced severe difficulties in the 1970's, and underwent a major restructuring. It is now a strong advocate for a major reorganization of the biotechnology activities in Swedish industry, and sees itself as playing a leadership role in this process. Volvo's Provendor Food Group accounted for 6.3 percent of total sales in 1985, and includes a new biotechnology company and two seed companies (see Table 5). In addition, Volvo has significant shareholdings in Pharmacia, KabiGen, and Sonesson (which owns Ferrosan, a pharmaceutical company), and attempted to acquire part of Fermenta. With Pharmacia's acquisition of Leo, Volvo is indirectly consolidating its position in the pharmaceutical industry, as well as in the separation technology sector. Ownership of Hilleshog, Weibull, and Sockerbolaget (Sugar Production Company) should allow Volvo to introduce new rDNA technologies into plant breeding and seed production (23).

HILLESHOG, a multinational industrial group, uses both rDNA and traditional plant breeding methods to produce varieties of agricultural crops, trees, and medicinal plants. It had total sales of SKr 912 million ($105.9 million) in 1985, and net profits of SKr 49 million ($5.7 million). Sixty-four percent of sales were abroad (24). Decreased profits in the Sugar Beet Seed Division sharply affected its performance in 1985.

Table 4.
Agreements with Pharmacia

Business Sector	Agreement
Pharmacia/Corporate	Volvo becomes majority stockholder - with 6.4% of stock and 26.6% of votes(1)
	Acquisition of Leo(2)
	Joint Venture with Alfa-Laval to form BioLink(2)
Biotechnology	Establishment of a genetic engineering research facility in La Jolla at an estimated cost of $5M/3 years(3)
	51% equity in Verax - cell culture technology(1)
Health Care	Joint venture with Chiron for production of human peroxide dismutase for treatment of heart disease(1)
	10.9% equity in Deltec - manufacturer of portable pumps(1)
Ophthamology	4.5% equity in Biotechnology General - production of hyaluronic acid by bacterial fermentation(1)
	2.2% equity in Biomatrix; also contract for new ophthamology products for viscosurgery(1)
	Acquisition of Intermedia Intraocular Optical lens company for SKr 500M(4)
Diagnostics	Agreement with Electro-Nucleonics for distribution of Pharmacia's Allergy and diagnostics products(1)

M = millions
1.Pharmacia Annual Report 1985.
2.Korsnas, Per, Pharmacia, personal communication, September 10, 1986.
3.Financial Times, London, September 29, 1986.
4.Financial Times, London, August 5, 1986.

Table 5
Volvo Investments in Biotechnology

Company	% Holding	Business Activities	1985 Sales in SKr
Provendor Food Group			
AC Biotechnics	100%	Microbial production of fine chemicals, waste water treatment	60M ($6.9M)*
Hilleshog	100%	Plant breeding, sugar beet seed	1000M ($116.2M)
Weibull	100%	Seed company	400M ($46.5M)
Holdings			
Pharmacia	6.4%	Pharmaceuticals, separation technology	3398M ($394.9M)
Sonesson	30%	Engineering, Pharmaceuticals	N/A
KabiGen	N/A	Genetic Engineering	

*Average exchange rate for 1985: SKr 8.6039 = $1.
M = millions

Hilleshog is organized into four divisions: Sugar Beet Seed, AgriSeed (cereals and oilseed rape), Forestry, and Research, and is acknowledged as having the best plant breeding research in Sweden. Its Research Division consists of four sections: Genetics and Breeding Methodology, Physiology and Biochemistry, Cell and Tissue Culture, and Secondary Plant Products. Considerable effort has been made in developing different techniques of gene transfer, such as cell fusion, hybridization, transfer into protoplasts, and the use of the Ti plasmid. The primary applications have been in rendering plants resistant to disease and to pesticides. In order to accomplish this, it is necessary to acquire a better understanding of plant physiology, as well as detailed metabolic pathways and the manner in which these are regulated. As part of an overall strategy, Hilleshog has acquired shares in biotechnology companies: 16 percent in Advanced Genetic Sciences in the U.S., 17 percent in Plant Genetic Systems in Belgium, and 35 percent in KabiGen. Hilleshog is collaborating with Advanced Genetic Sciences and DuPont to develop plant varieties that are resistant to sulfonylurea pesticides. Plant Genetic Systems is using rDNA techniques to render plants resistant to the virally-induced disease, Rhizomania. Both would be important developments for the sugar beet seed business (25).

Following Hilleshog's acquisition by Volvo, Weibull was integrated into the Hilleshog Group. A new strategic plan has been adopted, which will stabilize its sugar beet business and place stronger emphasis on plant-based, medicinal products. Hilleshog has:

- o acquired a majority holding in Convex Biotechnology in Denmark, which extracts pharmaceutical intermediates from plants;
- o acquired the seed operation of the Great Western Sugar Group, to expand its sugar beet operations in the U.S.; and
- o decreased its holding in KabiGen from 35 percent to 5 percent, because of the limited extent of KabiGen's plant research.

Further moves are expected as the Hilleshog Group becomes better integrated into the Provendor Food Group of Volvo.

New Biotechnology Companies

Sweden has a remarkably large number of small, new biotechnology companies (estimated at 15 to 20). Two of them, BioCarb and KabiGen, were studied in some detail.

BioCarb was founded in 1983 by four professors with SKr 30 million ($3.49 million) obtained from two Swedish financiers. This amount was later increased to SKr 75 million ($8.72 million). BioCarb is one of the few biotechnology companies involved in the production of complex carbohydrates. It has a staff of 50 and has contracts with 20 other scientists located in various universities. Annual sales average SKr 2.5-3 million ($290,500-$348,600), but annual R&D costs are approximately SKr 30 million ($3.49 million) (26).

BioCarb is organized into four sections: Separation, Organic Synthesis, Analysis, and Hybridoma. Principal business areas are diagnostics, therapeutics, and prophylactics. There are two subsidiaries: BioCarb Chemicals, which mainly sells complex carbohydrates to the research community, and MonoCarb, which produces monoclonal antibodies. These monoclonal antibodies have been used to develop new tests for blood grouping. An unusual product, developed in collaboration with Alfa-Laval, is an oligosaccharide for use in the treatment of mastitis in cows. While some of BioCarb's projects are in collaboration with larger, established companies, they also conduct their own research into the biological roles of the many complex carbohydrates found in humans.

KABIGEN is one of the few genetic engineering companies in Scandinavia, and is owned by four large companies: KabiVitrum (40 percent), Fermenta (45 percent), Hilleshog, and Nobel Industries. It has a staff of 50, and is organized into four groups: Organic Chemistry, Molecular Biology, Cell Biology, and Protein Chemistry (27).

At present, KabiGen conducts research for its parent companies and has an annual budget of approximately SKr 40 million ($4.65 million). Projects must be approved by the parent companies, which then have the option to commercialize them or make them available to external partners. KabiGen conducts research in three major research areas (27):

(1) Coagulation and fibrinolysis: cloning and expression of TPA, Factor VIII, and anti-thrombin III.

(2) Growth factors: cloning and expression of IGF-1, IGF-2, and prenatal growth factor.

(3) Gastrointestinal peptides: secretin and motilin.

One of the difficulties encountered by KabiGen is that TPA, Factor VIII, and anti-thrombin III are expressed in mammalian cells, but none of the parent companies has facilities for large-scale mammalian tissue culture. Fermenta and Hilleshog have indicated that neither has made significant commercial use of KabiGen's research findings. KabiGen has shown a high degree of scientific competence, but has been slow in translating its R&D into products and processes. Its further development depends on establishing closer relationships with its parent companies. Alternatively, it can actively seek external contracts or manufacture its own products.

Other Companies

The trials and tribulations of FERMENTA would provide excellent material for a TV miniseries. It has become a major multinational in the drugs/fine chemicals sector, and came very close to assuming the lead in the restructuring of the Swedish biotechnology industry. The Fermenta Group had sales of SKr 1,635 million ($190 million) in 1985, with a net profit of SKr 320 million ($37.2 million) (28).

Mr. Refaat El-Sayed, the Chief Executive Officer (CEO), and major shareholder of Fermenta, identified a profitable niche in the production of bulk basic antibiotics and their intermediates (29). The earnings of such operations was used to acquire the new technologies of genetic engineering and monoclonal antibodies that were then applied to existing pharmaceutical, animal health care, and agrochemical businesses. (Table 6 provides a brief summary of the moves made by Fermenta to implement this strategy.)

The first two of Fermenta's objectives were carried out successfully. Purchase of raw materials, rationalization of production, and improvement of production technology were planned to maximize both productivity and profitability. This rapid expansion was financed by selling off peripheral activities of acquired firms, and by payment with newly issued Fermenta shares. Fermenta has been partially successful in meeting its third objective, by buying 3 U.S. companies in the agrochemical and human health care areas. Serious difficulties arose when it tried to gain control of a major segment of the Swedish pharmaceutical industry (30). Following unsuccessful negotiations to acquire KabiVitrum, Fermenta agreed to buy Volvo's minority interests in Pharmacia and in Sonessons (owner of Leo and Ferrosan drug companies) in a deal estimated to be worth more than SKr 4 billion ($464.9 million). Volvo held 5.1 percent of Pharmacia's equity, and 21 percent of its voting shares, while 3 investment firms closely associated with Volvo held a further 6 percent of the equity and 19.2 percent of the votes. In return, Volvo would have received 20-25 percent of Fermenta's shares. Soon after announcement of this agreement, it was discovered that Mr. El-Sayed lacked the academic credentials he had claimed, and in the ensuing scandal, Fermenta's share price dropped precipitously, leading to Volvo's cancellation of the agreement. Mr. El-Sayed was forced to step down as CEO, and subsequently, Fermenta came close to expulsion from the Stockholm Stock Exchange. Fermenta was severely reprimanded and the maximum fine imposed. Mr. El-Sayed has sold 32 percent of his shares to 2 Swedish investment firms, Beijer and Industrivaerden, and the state holding company, ProCordia. He is currently under investigation for insider trading. Following the collapse of the Volvo deal, the Italian multinational, Montedison, entered into negotiations to purchase Mr. El-Sayed's shares (44 percent of the equity and 78 percent of the votes) for a reported SKr 3 billion ($348.7 million). After 5 months of negotiations, Montedison withdrew its offer and accused Mr. El-Sayed of altering the shareholding structure and other terms relating to the original agreement. Mr. El-Sayed is said to be seeking a closer relationship with ProCordia, which has agreed to two further options with Mr. El-Sayed, each permitting the purchase of a further 1.5 million shares. The first option must be exercised within 12 months, the other by September 1988.

Mr. El-Sayed is now expected to reorganize Fermenta. He is currently negotiating a deal, understood to be worth $215 million, with Monsanto for the sale of the bulk of Fermenta's agrochemicals interests (31).

Given Fermenta's major impact on Swedish biotechnology, it is evident that the restructuring of this industrial sector must await settlement of the present crisis.

Table 6.
Summary of Fermenta's Activities

Objective	Implementation
I. Establishment of a profitable business in production of bulk antibiotics & intermediates	1982-86 Acquisition of 4 fermentation facilities in Italy, 1 in Sweden, 1 in the U.S.; acquisition of 1 organic synthesis company in France 1984-85 Joint ventures in Mexico, South Korea, Taiwan, Ireland, India & Egypt
II. Access to New Biotechnology	1985 Gradual acquisition of 45% of KabiGen 1985 Acquisition of 9.7% of Amgen
III. Establishment of new business sectors with intention of applying new biotechnology	
A. Pharmaceuticals	1985 Attempt to acquire KabiVitrum 1986 Unsuccessful attempt to acquire Volvo's minority interests in Pharmacia & Sonesson (parent of Leo & Ferrosan) 1986 Acquisition of Pierre, an Italian pharmaceutical company
B. Animal Health Care	1985 Acquisition of SDS Biotech & reorganization into Fermenta Animal Care & Ricerca, an R&D company 1986 Acquisition of Techamerica, U.S. animal health care company
C. Agrochemicals	1985 Acquisition of Vertac's Agrochemical business 1985 SDS Biotech reorganization to form Fermenta Plant Protection

Skandigen is a venture capital organization with the objective of investing in applied research in universities, and in financing the formation of new biotechnology companies. It also encourages joint ventures between its associated companies.

In unusual cases, Skandigen will fund new projects in established companies. As the projects reach the point of commercialization, Skandigen will sell or license these new processes to larger companies for production. Concentration has been in two project areas: (1) large-scale, continuous cultivation, and (2) downstream processing for purification of biological products.

Skandigen was formed in 1983, with an individual investment of SKr 40 million ($4.65 million), which has now grown to SKr 200 million ($23.3 million). It had sales of SKr 200 million ($23.3 million) in 1985, and losses of SKr 9.1 million ($1.06 million). Skandigen has a portfolio of 12 companies: 8 in Sweden, 2 in the U.S., and 1 each in the U.K. and Switzerland. Thirty-nine percent of its investments are in Sweden and 69 percent are abroad (32). Principal projects are (33):

- production of human antithrombin (initiated with Genentech),
- production of peptide hormones (in collaboration with KabiGen),
- production of human albumin by chemical synthesis, and
- technique for industrial production of edible morels.

Skandigen considers the potential for new products and processes particularly high in Sweden, but these are unlikely to be exploited by established companies until developed to the commercial stage.

INDUSTRIAL OVERVIEW

Sweden's position in biotechnology is strongly dependent on its industrial sector, which consists of a number of medium-sized multinationals with well established niches (the major Scandinavian industrial group), and a stable of small, new biotechnology companies. These companies are generally well matched to the strongest research areas in the universities, and university-industry interactions are very good. The general environment for industrial development is favorable, with support from the government (mainly from the STU), and capitalization from financial organizations and venture capital funds.

On the other hand, Sweden does not have a major multinational pharmaceutical or chemical corporation on the scale of Ciba-Geigy or AKZO. Most of the established companies have been slow in recognizing the importance of the new biological technologies with serious consequences (e.g., KabiVitrum's withdrawal of hGH from the market), and have only recently moved to gain access to them. The small biotechnology companies have been more aggressive in developing new products and processes, primarily directed towards the pharmaceutical market, but their future remains uncertain unless they can enter into joint ventures with established companies or are acquired by them. The NRF and the Swedish Industry Committee for Biotechnology are

trying to educate the Swedish industrial and financial community as to the potential of biotechnology, and therefore create a supportive environment for further growth.

Though part of the Swedish industrial establishment believes that the Fermenta debacle may have a dampening effect on biotechnology, it nevertheless served to illustrate that an imaginative and aggressive consolidation in that sector could create a profitable, internationally competitive, industrial group. It is important to note that in spite of the lip service given to the Nordic bloc, the emphasis of the Fermenta strategy was on production facilities and markets in the EEC and the U.S., with potential capitalization from those same countries. The current upheaval at Fermenta will, at the very least, delay the implementation of its business plans, but is unlikely to change Volvo's long-term plans in the same direction.

V. CONCLUSION

As the biological revolution enters its industrial phase, Sweden finds itself in a strong position. Its research and university establishment is the best, and largest, in Scandinavia. The same is true of its industrial and financial sectors. It is this preeminent position, vis-a-vis other Nordic countries, that can lead to a dangerous complacency, particularly as international competition rapidly increases. In a sense, Sweden's base line for comparison should lie with countries such as the Netherlands and Switzerland, both small nations with well developed industrial and commercial sectors.

Swedish government policy has been active in promoting technology transfer and industrial innovation, particularly through the STU. Expenditures for university education and research have been adequate, but not overgenerous. This is reflected by the fact that while basic research is traditionally strong in protein and carbohydrate chemistry, separation methodology, and biochemical engineering, Sweden has been relatively weak in the more biological areas, such as microbiology, eukaryotic gene expression, genetics, and plant molecular biology. Many Swedish experts feel that there has been too much emphasis on applied research and technology transfer, and that it is time the government expanded its efforts in basic research. The STU has put into place a program to build up expertise in genetic engineering, and the new National Program in Biotechnology should make additional funds available for biological research. The manpower pool in biotechnology is perceived as limited, particularly in the biological areas. This problem is accentuated by difficulties in recruiting foreign scientists to work in Swedish laboratories (presumably due to low salaries and high taxes).

The regulatory situation in Sweden is considered good, following the lifting of a moratorium on rDNA work in 1982. The regulations appear to be similar to those presently in effect in the U.S. The political situation has eased since the environmental movement has directed its attentions to nuclear power, following the Chernobyl disaster. It is likely that new regulations, directed towards effluents from facilities using rDNA technology and towards the release of genetically engineered plants and microorganisms, will be proposed during the next 2 years.

As indicated previously, Swedish industry is in a favorable situation at the present time, but there are important issues that must be resolved if it is to retain this competitive edge. Heavy dependence on instrumentation, engineering, and physical methods, make Sweden vulnerable in a field that is quintessentially biological. This bias is further accentuated by the fact that the universities are also weak in many of the same biological research areas. As in the U.S. and the U.K., small, new companies play an important role in introducing new technologies and products, but it is not clear whether they can flourish in the Swedish environment.

As foreign companies challenge traditional markets, the major Swedish biotechnology companies are under pressure to develop strategic alliances and to consolidate. Both Volvo and the major financial institutions encourage this trend in order to create industrial groups that can compete in international markets, particularly in pharmaceuticals, agrochemicals, and food processing. Alfa-Laval is well placed, following its acquisition of Chemap and its joint venture with Pharmacia. Fermenta's basic business is sound, but its attempt to take over a significant part of the Swedish pharmaceutical industry is probably doomed to failure. This does not preclude major changes in the agricultural and food sectors. Regardless of the precise form of future developments, it is likely to involve continued acquisitions and agreements in the U.S. and EEC countries, in order to obtain production facilities and access to advanced R&D.

ACKNOWLEDGMENTS

Catharina Kronstrom, Marketing Consultant, Foreign Commercial Service, American Embassy, Stockholm.

REFERENCES

1. Quarterly Economic Report on Sweden, American Embassy, Stockholm, June 11, 1986.

2. 1984 Research Policy Bill, translated by Roger G. Tanner, Swedish Institute, document no. 319, June, 1984.

3. Af Malmborg, Charlotte, Swedish National Board for Technical Development, personal communication, September 10, 1986.

4. Broman, Svetlana, The National Industrial Board, personal communication, September 9, 1986.

5. Teknik I Tiden No. 5, 1984.

6. Enfors, Sven-Olof, Royal Institute of Technology, personal communication, September 11, 1986.

7. Zomzely-Neurath, Claire, Biotechnology in Sweden, published by Office of Naval Research, London, June 10, 1985.

8. Svenska Dagbladet, March 22, 1985.

9. Dagens Nyheter, June 1, 1985.

10. Haska, Guno, Biotechnology Research Foundation, personal communication, September 12, 1986.

11. Biotechnology Research Foundation Scientific Report, 1982-85.

12. Kronstrom, C., Biotechnology Market Assessment, American Embassy, Stockholm, July 3, 1986.

13. SCRIP, March 5, 1986.

14. Financial Times, London, June 4, 1986.

15. SCRIP, March 5, 1986.

16. Alfa-Laval Annual Report 1985.

17. Alfa-Laval Annual Report 1985.

18. Rosen, Carl-Gustaf, Alfa-Laval, personal communication, September 11, 1986.

19. LKB Annual Report 1985.

20. Bishop, Roger and John Ptak, LKB, personal communication, September 9, 1986.

21. Pharmacia Annual Report 1985.

22. Financial Times, London, August 5, 1986.

23. Volvo Annual Report 1985.

24. Hilleshog Annual Report 1985.

25. Bornman, Chris H., Hilleshog, personal communication, September 12, 1986.

26. Sjoberg, Peter and Alan Chester, BioCarb, personal communication, September 12, 1986.

27. Lind, Peter, KabiGen, personal communication, September 8, 1986.

28. Fermenta Annual Report 1985.

29. Gatenbeck, Sten, Fermenta, personal communication, September 9, 1986.

30. The Economist, September 13, 1986.

31. Financial Times, London, October 23, 1986.

32. Skandigen Annual Report 1985.

33. Aberg, Bertil, Skandigen, personal communication, September 9, 1986.

34. Larsson, Lennart, Association of Swedish Chemical Industries, personal communication, September 8, 1986.

APPENDIX

ORGANIZATIONS AND INDIVIDUALS VISITED

GOVERNMENT

The National Industrial Board: Mrs. Svetlana Broman, Senior Project Manager, Industrial Development Department.

Swedish National Board for Technical Development: Mrs. Charlotte Af Malmborg, Head of Medical, Welfare and Life Sciences Department.

UNIVERSITIES AND RESEARCH INSTITUTES

Royal Institute of Technology: Professor Sven-Olof Enfors, Department of Biochemistry and Biotechnology.

Biotechnology Research Foundation: Dr. Guno Haska, General Manager.

INDUSTRY

Association of Swedish Chemical Industries: Dr. Lennart Larsson, Secretary.

Alfa-Laval: Dr. Carl-Gustaf Rosen, Research Director, Industrial Biotechnology; Ms. Ann-Marie Gronberg, Information Manager.

BioCarb: Mr. Peter Sjoberg, Managing Director; Dr. Alan Chester, Project Director.

Fermenta: Dr. Sten Gatenbeck, Vice President for Research and Development.

Hilleshog: Professor Chris H. Bornman, Section Head.

KabiGen: Dr. Peter Lind, Scientist, Molecular Biology.

LKB: Dr. Roger Bishop, Manager, Scientific Support Division; Dr. John Ptak, Marketing Manager, Biotechnology Division.

Pharmacia: Mr. Bengt Bentzer, Public Affairs; Dr. Per Korsnas, Scientist, Biotechnology Division.

Skandigen: Dr. Bertil Aberg, President.

SECTION H

BIOTECHNOLOGY IN SWITZERLAND

SUMMARY

In Switzerland, there is little concerted effort on biotechnology between the government, universities, research institutes, and private companies. The largest proportion of R&D is carried out by the three major pharmaceutical companies, while fundamental research is centered around the universities and certain research institutes funded by the pharmaceutical industry. The federal government's role is to coordinate various aspects of science policy including international agreements, fund basic research and the two federal institutes of technology, and subsidize the cantonal universities. While Switzerland's position in biotechnology is highly competitive because of its research base, industrial capabilities and manpower pool, the industrial application of these new technologies has not been pursued aggressively.

I. INTRODUCTION

Switzerland is a prosperous, industrial nation of some six million inhabitants. It has the highest per capita income among the industrial nations. Its economy is dependent on international trade and has shown steady growth for the past 2 years. It is also the U.S.'s sixth largest export market in Western Europe and is important both as a producer and as a market in high technology products.

The political structure of Switzerland is unusual in that most of the power resides in the cantonal governments rather than in the federal government in Bern. Two-thirds of all government expenditures are made by cantonal and local governments with the remaining third by the federal authorities.

As relates to biotechnology, Switzerland is in an excellent position with an important research establishment based in universities and in research institutes funded by private industry. In the industrial sector, it counts with some of the most important multinationals in the pharmaceutical/chemical sector: Ciba-Geigy, Hoffmann-La Roche, and Sandoz.

(In order to assess the current status of biotechnology in Switzerland, the author had 16 meetings with key individuals involved in Swiss biotechnology.)

II. GOVERNMENT POLICY

Unlike most of her European neighbors Switzerland does not have a government policy to promote biotechnology. Swiss science is highly decentralized and it is estimated that 75 percent of all Swiss R&D [estimated at SwF 3 billion ($1.22 billion)]* is done in industry (1). The role of the

*1985 average exchange rate: Swiss franc (SwF) 2.457 = $1.

federal government is directed towards the support of basic research and education. The two most important agencies are the Federal Office of Education and Science [Bundesamt fur bildung und Wissenschaft (BBW)] and the Swiss National Fund for the Promotion of Scientific Research [Schweizirischer Fonds fur Forderung der Wissenschaftlichen Forschung (SNF)].

1. Federal Office of Education and Science: This is one of the offices of the Federal Department (Ministry) of the Interior with a 1985 budget of SwF 591.8 million ($240.9 million) (2). It provides support and coordination for research policy to the Federal Council (the Council of Ministers that determine federal policy) and implements and coordinates international research agreements primarily within the framework of the EEC (European Community) and the Eureka program. In the area of biotechnology, the most important of these international programs are:

> COST (Committee on Science and Technology): joint projects between EEC countries and non-EEC European countries.
>
> European Molecular Biology Conference: primarily provides stipends for training and research in molecular biology.
>
> European Molecular Biology Laboratory: support for the international laboratory for molecular biology located in Heidelberg.
>
> UNIDO (United Nations Industrial Development Organization): support for the UNIDO laboratories for Genetic Engineering in Trieste and New Delhi.

The total Swiss contribution for these activities is in the order of SwF 5 million ($2.03 million) (2). Potentially, the influence of this Office could have increased with the creation of National Research Programs as defined by the Federal Council and funded by the SNF (see below). A far more important function is the financial support of centers of higher learning where most basic research laboratories are located. Switzerland has eight cantonal universities. In addition, there are two Federal Institutes of Technology (ETH) located in Zurich and Lausanne. These were originally created to provide specialized training in engineering and the sciences. The federal government funds the ETH-Zurich [1985 budget: SwF 314.6 million ($128 million)] and the ETH-Lausanne [1985 budget SwF 113.4 million ($46.2 million)] (2). In addition, it subsidizes the budgets of the cantonal universities [total budget of SwF 1.38 billion ($562 million)] (2). It contributes 40-45 percent of capital investments (the proportion varying somewhat according to the wealth of the canton) and 15-16 percent of the operating costs (including salaries, materials and supplies). In exchange for its financial support, the Confederation gets a better coordination of research and education in the universities. The Swiss University Conference (Schweizerische Hochschulkonferenz) acts as the main intermediary between the federal government and the cantons in matters of higher education, a sensitive task given the strong political support for local autonomy.

2. Swiss National Fund for the Promotion of Scientific Research (SNF): In the eyes of many, this is the most important government organization involved in science. It is organized as a private foundation that derives 99 percent

of its funding from the federal government (3). Its 1985 budget was SwF 172 million ($70 million), and it is organized into four sections which share the budget in the following manner (3):

I. Humanities and Social Sciences: 16 percent

II. Exact and Natural Sciences: 35 percent

III. Biology and Medicine: 37 percent

IV. National Research Programs: 12 percent

Most of the biotechnology related research would fall into category III. Various Swiss scientists have pointed out that in the absence of defined priorities, the only funding policy has been that of scientific excellence independent of research area. This has promoted quality research at the major Swiss universities.

The federal government established the National Research Programs in 1975. Under this scheme, part of the SNF budget would be reserved for research into problem areas of national importance as defined by the Federal Council. Each program would be funded for some SwF 8-15 million ($3.3-$6.1 million) for a period of 5 years (4). Since the BBW did not have the statutory authority and there was no consensus within the SNF to promote biotechnology, it was conceivable that the National Research Programs could have provided a mechanism to do so. This has not turned out to be the case. The problems selected by the Federal Council have been of a non-controversial nature falling into the following categories:

- o ecology: e.g. the water cycle, socio-economic development in the mountains;
- o social sciences: e.g. cultural pluralism in Switzerland; and
- o public health: e.g. prophylaxis of cardiovascular diseases, biomedical technology.

3. Commission for the Promotion of Scientific Research: This commission is charged with the responsibility of stimulating applied R&D. However, its 1985 budget of SwF 17 million ($6.9 million) (2) is relatively small, and does not seem to have made much of an impact on biotechnology (see below).

The Swiss system has been effective in supporting good basic research in the universities both directly through SNF grants and indirectly by subsidizing university budgets. A third of the total university budgets is spent in research (3). Even though important individuals in the government, industry and universities have expressed support for a more selective support of basic research consistent with industrial development, there is nothing to indicate that there is a broad consensus for this view. Rather, there is a strongly held view that commercially relevant R&D should be carried out by the private companies.

III. UNIVERSITIES AND RESEARCH INSTITUTES

Government supported research is centered in the universities. The first molecular biology department was established at the University of Geneva in the 1960's, and this was followed by two departments of Molecular Biology at the University of Zurich, an Institute of Biotechnology at ETH-Zurich, and a new Biozentrum (composed of six biological departments) at the University of Basel.

(a) Financial Support: The federal budget deficit (an issue to which the Swiss are more sensitive than most) has resulted in a fairly constant SNF budget (5):

1983	SwF 162.4 million	($66.1 million)
1984	SwF 154.6 million	($62.9 million)
1985	SwF 172 million	($70 million)

Of the 37 percent that goes to Biology and Medicine, roughly two-thirds is for medicine (5). Most of the remaining third is spent on basic projects, and an examination of individual projects would indicate that less than half could be even loosely interpreted to be in biotechnology. The effect of constant budgets has been both a reduction in the number and amount of grants awarded. At the same time, there has been a freeze in positions funded by the SNF and in the staff of the ETH's. The situation at the ETH's had become so serious, particularly in growing fields such as biotechnology, that 50-100 new positions will be created to deal with this problem (6).

The cantonal universities have the advantage of substantial research funding from the canton. For example, a 1982 analysis of the operating costs (salaries plus materials and supplies) of the Biozentrum of the University of Basel showed that 86 percent was paid by the canton, 13 percent by the SNF and the remaining 1 percent by other sources (mostly industry) (6). Nevertheless, budgetary constraints in the canton have led to a staff reduction of 10 percent and a reduction in operating budgets of 3.5 percent (6). Though the scientists have been increasingly critical of this decrease in financial support, the general consensus is that Swiss biological research continues to be funded at a generous level, and with very few strings attached. The major cause for concern is the inability to hire new people in order to meet new research needs.

(b) Scientific Research: Switzerland has a good research base in the biological sciences particularly in those areas where they had an early start, e.g., bacterial and phage molecular genetics, virology, developmental and cell biology, and immunology. Table 1 gives an overview of some of the principal research activities at several of the major university laboratories. The overall impression is one of quality research on important scientific problems. However, there is little evidence of coordinated research efforts or of any major emphasis on biotechnology applications except at the ETH-Zurich and the University of Zurich. Switzerland has been much slower in applying the new techniques of molecular biology and cell culture to plants,

185

Table 1.
MAJOR RESEARCH LABORATORIES VISITED

	BIOZENTRUM University of Basel	INSTITUTE OF MICROBIOLOGY University of Geneva	INSTITUTE OF BIOTECHNOLOGY ETH/Zurich	DEPARTMENTS OF MOLECULAR BIOLOGY I & II University of Zurich
SELECTED RESEARCH THEMES	Structure & function of yeast mitochondria Developmental biology of Drosophila Structural studies of model & biological membranes Kinetics of enzymatic reactions Molecular biology of phage T4 Development of electron microscopy methods Transposition & genome rearrangements in E. Coli Mechanisms of restriction & modification enzymes	Mechanism of the immune response Molecular biology of major histocompatibility locus	Mass cultivation, scale up & process developments Fermenter design Enzymology: immobilization & enzyme alteration	Developmental biology of amphibians Structure & function of interferons Molecular biology of scrapies

fermentation and downstream processing. It was partly in order to meet this challenge that the Institute of Biotechnology was established at ETH-Zurich in 1981. It has a total of 40 people, of which 13.5 positions are staff, and has an annual budget of several million SwF (1). Its two main research areas are biochemical engineering and applied biochemistry. Early on, it had collaborated with Biogen on production of alpha and gamma interferon. A great deal of its current effort is directed towards new fermenter designs and sensors for such compounds as ethanol and oxygen. The view was frequently expressed that the research program is not very innovative and did not put sufficient emphasis on bacterial genetics and physiology, nor on new approaches to downstream processing. It is also felt that there are limited interactions with the Departments of Molecular Biology I & II of the University of Zurich which are located on the same campus (to create a biological research complex).

Local autonomy and scientific freedom have allowed individual researchers to do some of their best work without interference, subject only to peer review. Therefore, there is a general consensus in support of the present system. The minority view is that the present system does not deal with the more applied aspects of biotechnology research.

(c) University-Industry Interactions: Since cantonal funding of research is highly significant, it has always been important for academic researchers to maintain good relationships with industry. This is relatively easy to do given the small and cohesive nature of Swiss society. As regards biotechnology, industry means the three big pharmaceutical companies which not only have their own corporate R&D, but also support private basic research institutes. Therefore, they prefer that the universities restrict their activities to basic research and education, and stay away from technology transfer.

University-industry relations take the following forms:

(1) Informal, ad hoc arrangements: an investigator may get gift of computer time or a run on a fermenter or support for a conference, negotiated on a case-by-case basis.

(2) Consultantships: academics may act as consultants to industry.

(3) Student Support: this is one of the most common forms of industrial involvement with a company paying the salary of a graduate student.

(4) Foundation Support: the pharmaceutical companies have foundations which can provide financial assistance in the form of grants and stipends. The sums involved are relatively small; e.g., a recent Ciba-Geigy Foundation award of SwF 150,000 ($61,000) for 2 years was the largest ever given by them (6).

Therefore, there are no real mechanisms for technology transfer from university, nor any apparent interest in it from either the scientists or the companies. This is even true in the case of Chemap, a manufacturer of fermentation equipment, which participates minimally in the activities of the

Institute of Biotechnology. The sole exception is the existence of a Biogen laboratory at the University of Zurich, which is clearly due to the presence of Professor C. Weissman, one of the company's founders, in the factory. Aside from Biogen, there is little interest in the creation of new biotechnology companies.

(d) Staffing: The Swiss avoided many academic battles associated with recruiting new scientific groups by simply establishing new departments or centers, i.e. the Departments of Molecular Biology at Geneva and Zurich, the Institute of Biotechnology at ETH-Zurich, and the Biozentrum in Basel. This large expansion at the end of the 1960's and beginning of the 1970's could not be carried out with only Swiss scientists. The good salaries, favorable work environment, and attractive quality of life, served to attract foreign scientists at all levels and in most project areas. Tradition and the international nature of most key Swiss labs makes this a straightforward solution to manpower problems.

(e) Education: The Swiss have always accepted the need for high quality scientific and technical training as one of the requirements for industrial development. The creation of new departments made it easier to establish new undergraduate and graduate programs. The undergraduate degree (the diploma) takes about 4-6 years. The Basel curriculum consists of 2 years of basic sciences followed by 2 years of more specialized courses such as microbiology, biochemistry, biophysics, and structural biology. Then follows 1 year of experimental work on a lab project. This provides an excellent background both for industry and for further studies towards a Ph.D. Depending on the department, this may require some additional course work, plus research for a doctoral thesis. A Ph.D. would take 3-4 years work beyond the diploma. Most Swiss Ph.D.'s usually do postdoctoral work in the U.S., but occasionally in France or Germany. Therefore, the length of training in Switzerland is roughly the same as in the U.S. and its quality is likely to be as good as any. The success of this system makes it much easier to maintain local support for the universities and their research activities.

An unusual development has been the creation of basic research institutes funded by pharmaceutical companies both in Switzerland and abroad. Usually, the institute has a charter that defines its research areas, while its policies are determined by a board of directors, that has a significant corporate representation. The institute is run by a director who is then responsible to the board. In principle, these institutes are free to pursue their research subject to scientific review and independently of the commercial needs of the corporate parent. In practice, both the board and the director should be sensitive to corporate concerns and strategies. Table 2 gives a summary of the major institutes and their principal research themes.

Basel Institute of Immunology (BII): Hoffmann-La Roche has three research institutes around the world: the Roche Institute of Molecular Biology (Nutley, N.J.), the Nippon Roche Research Center (Kamakura, Japan), and the Basel Institute of Immunology. The description in this study of the center is dependent upon published accounts and other scientific and corporate contacts (an on-site visit could not be arranged). The BII has a staff of 200, of which 63 are scientists and the remainder technical and administrative

BLANK PAGE

Table 2.
SWISS RESEARCH INSTITUTES

	Basel Institute of Immunology	Friedrich Miescher Institute	Battelle Institute
	Roche	Ciba-Geigy	Battelle Institute (USA)
Research Themes	Mechanisms of antibody diversity Structure and rearrangement of Ig genes Structure of MHC genes Genes for T-cell receptors Lymphocytes activation & differentiation Lymphokines	Replication & expression of Cauliflower Mosaic Virus (CAMV) Plant transformation using CAMV Hormonal regulation of specific eukaryotic genes N-ras oncogene function Hormonal regulation of plasminogen activator Modulators of neuronal behavior Mechanisms of embryonal cell differentiation	Development of light-sensitive promoters in animal cells Development of non-radioactive DNA probe diagnostic systems Development of biodegradeable polymers Genetic engineering Electrical fusion of animal, plant, & bacterial cells Inhalation therapy
Affiliated Institutes	Roche Institute of Molecular Biology (Nutley, N.J., USA) Prokaryotic molecular biology, immunomodulators, molecular biology of smell, animal viruses Nippon Roche Research Center (Kamakura, Japan) Pharmacokinetics formulation, applied microbiology, cancer biology	Agricultural Biotechnology Center (Triangle Park, N.C., USA) Plant biology	Battelle Memorial Institute (Columbus, Ohio, USA) Battelle Institute (Frankfurt, Federal Republic of Germany)

NOTE: Sandoz maintains an institute in Vienna.
Activities: Infectious diseases, immune mediators, proteases, cancer biology.

personnel (7). It is an internationally recognized center for immunological research and has made major contributions to this field.

Though the Institute functions as a basic research organization, the rapid development in immunology raised the possibilities of new naturally occurring drugs (e.g., interferon) and therapies and a need for some form of technology transfer to the corporate side. At the same time, the Institute of Molecular Biology moved aggressively into the cloning and expression of eukaryotic genes in E. coli. This created a complex management problem involving two autonomous research institutes, corporate R&D in the U.S. and Switzerland, and the pharmaceutical division. One partial solution was to convince one of the groups to transfer to corporate R&D in order to form the nucleus of an Applied Immunology Department. As will be seen in the next section, this proved to have mixed results.

Dr. Niels Jerne was director of the BII from 1969 to 1980. Dr. Fritz Melchers succeeded him in the fall of 1980. In 1984, Dr. Jerne received the Nobel Prize in Medicine along with Dr. George Kohler, one of the senior members of the institute. At the time, Dr. Kohler had already accepted a directorship at the Max Planck Institute for Immunobiology in Freiburg, FRG. It is the view of some that while the Institute retains its ability to carry out excellent research, it is now in a transition period under new leadership. It faces the dual challenge of no longer being unique while facing active competition from other institutes doing similar research and at the same time deciding whether to continue to operate independently of the Institute of Molecular Biology and corporate R&D.

Friedrich-Miescher Institute (FMI): Ciba-Geigy supports the Friedrich-Miescher Institute in Basel and the Agricultural Biotechnology Center in North Carolina. The FMI has a staff of 140, of which 80 have Ph.D.'s, and an annual budget of SwF 50 million ($20.4 million) (8). In the case of the FMI as well as the other institutes, this figure is probably an underestimate since the corporation provides services and materials free of charge.

The FMI has had a checkered past since its establishment in 1970. Its research has always been of a broader spectrum than the BII and its general directions have reflected the interests of its director (a search is underway for its fourth one). Initially, it had a biochemical bias and was directed towards protein synthesis. Then, it shifted towards mammalian cell biology, and more recently towards plant molecular biology. Dr. Heusler, the Acting Director, stated that the theme of the Institute is regulation of gene expression and that it will maintain an even mix of basic molecular biology, mammalian cell biology and plant molecular biology. The principal research themes appear in Table 2.

As in the case of the BII, there are very few tenured members on the staff. The research groups at the FMI may obtain additional funding from external sources such as the SNF and the European Molecular Biology Organization (EMBO). Staff members expressed the view that the main problem is the ambiguity of the relationship between the FMI and its corporate parent (the Institute is physically adjacent to the production facilities), which could affect the long-term stability of individual research groups.

Battelle Research Institute: This Institute is part of the Battelle Institute of Columbus, Ohio, the world's largest not-for-profit contract R&D organization. As indicated in Table 2, there is also another Battelle Institute in Frankfurt. All three of them have biotechnology departments, but the largest is in Columbus. The Geneva institute has a staff of 400. Ninety-five percent of its contracts are with private industry with 80 percent of the projects having been initiated by Battelle (9). This means that the institute has to invest its own money to start up many of the projects. This internal funding is controlled by the director, but it mainly originates with the main institute in Columbus.

As shown in Table 2, most of the research areas are sharply defined in terms of products and/or processes. Battelle provides services in genetic engineering, but the most important area is inhalation toxicology primarily working with rats and hamsters. This is an extremely expensive area and costs are approximately SwF 300,000/month ($117,000) (9). Another important area is the development of new chemical separation methods for biological compounds.

Biotechnology represents an important growth area for the Institute. Given the cautious nature of Swiss corporations, they are unlikely to invest heavily in R&D in new technologies. A large organization such as Battelle, provides them with R&D capabilities at defined costs and with full confidentiality. The sponsor usually retains the rights to the research findings. The only major limitation is whether the Institute will be willing to start projects in high risk areas prior to industrial sponsorship in order to stay ahead scientifically.

IV. INDUSTRY

Biotechnology activities in Switzerland are concentrated in three major pharmaceutical/chemical groups. These three corporate groups were visited along with Biogen, one of the earliest biotechnology start-up companies and also one of the most important. The most important activities are in pharmaceuticals, followed by agricultural chemicals and animal health care. All three major corporations are multinational, highly profitable (1985 was one of their best years), and have major commitments to R&D.

CIBA-GEIGY is one of the world's largest corporations (ranks 51 among the Fortune 500) (10), and its pharmaceutical division is fifth among the world's top drug companies. It had annual sales for 1985 of SwF 18.2 billion ($7.4 billion) with profits of SwF 1.47 billion ($598 million) (11). Its business is divided into these sectors (11):

Dyestuffs and chemicals:	14 percent of sales
Pharmaceuticals:	29 percent
Agricultural:	26 percent
Plastics and additives:	21 percent
Airwick:	4 percent (sold at the end of 1984)
Ilford (photography):	3 percent
Electronic equipment:	3 percent

The two most important activities are pharmaceuticals, whose sales have increased by 11 percent from last year, and agricultural products with a similar increase (11). The corporate strategy is directed towards taking advantage of the continuing growth of the pharmaceuticals sector while expanding into the agricultural sector. These efforts coincide with expansion of business activities in the U.S.

Of the three major pharmaceutical/chemical groups, Ciba-Geigy seems to have made the most serious commitment to biotechnology. Since there is no central R&D, biotechnology activities are concentrated in the Pharmaceutical and Agricultural divisions. The Biotechnology Department of the Pharmaceutical Division has a staff of 200, of which 52 are Ph.D.'s (12). Some of the groups work on microbiology, fermentation and process engineering primarily directed towards the traditional tasks of isolating and improving strains and increasing productivity in the preparation of antibiotics. Some 50 percent of the staff is involved in genetic engineering directed towards two major areas (12):

(1) Cloning and production of new drugs such as alpha-interferon (possible treatment of cancer and viral infections), tissue plasminogen activator (for treatment of blood clots), and insulin-like growth factor, and

(2) Cloning and production of protease inhibitors (these are being tested for therapeutic uses, e.g. eglin for emphysema, hirudin for inhibition of thrombin).

In addition, there is:

(3) Plant tissue culture of alpine plants (isolation and testing of secondary metabolites for pharmacological activity).

In the Agricultural Division, some of the basic research is done at the Friedrich Miescher Institute, while the more applied projects are done at the new center in North Carolina which now has a staff of 50 (11). The principal objective is to develop methods to work with plant cells in culture so as to modify the characteristics of crop plants. They have developed a novel liquid suspension cell culture system for regenerating cotton plant embryos -- an essential step towards producing plants with uniform characteristics. Equally important projects are biological pesticides (development of recombinant DNA viruses to destroy moths that attack pine trees) and animal health care (development of bovine interferon for treatment of shipping fever).

In addition to their own corporate efforts, Ciba-Geigy has made effective use of external agreements to obtain technologies, processes, and business outlets that they lacked. Table 3 summarizes agreements made last year. Though some of these activities are in support of the protease and ILGF projects, most of the effort appears concentrated towards long-term development of the new technologies necessary for agricultural innovation.

Table 3.
CIBA-GEIGY AGREEMENTS

Company	Nature of Agreement	Project	
		Pharmaceutical	Agricultural
ETH-Zurich	Support of university research		Microbial degradation of wastes from pesticide production
Agricultural Genetics Co.	Contract		Transposition in plants
Agridiagnostics Associates	Contract		Monoclonal antibody kits for fungal diseases of horticultural plants & crops
Bio-Response	Contract	Production of proteins from cell lines	
Biostar	Contract		Testing of bovine interferons
Calgene	N/A		Plant area
Chiron	Contract	Production of insulin-like growth factors	
Genentech	Exclusive rights		Bovine interferon & other animal health products
Plant Genetic Systems	N/A		Plant area
Twyford	N/A		Plant area
Unigene	Contracts	Research on protease inhibitors for therapy	
Corning Glass	Joint venture	Creation of Ciba Corning for manufacture of diagnostics	
Agricultural Genetics Co.	Shareholding		Agricultural R&D
Hartman's Plants	Acquisition		Specialists in regeneration of plantlets from tissue
Ring Around Products	Acquisition		Corn & sorghum seed business

N/A:information not available at the time of printing.

HOFFMANN-LA ROCHE is one of the largest pharmaceutical companies (11th in world sales) (13) with an annual sales of SwF 8.94 billion ($3.64 billion) with profits of SwF 451.6 million ($183.8 million) (14). Its operating divisions are (15):

Pharmaceuticals:	42 percent
Vitamins and fine chemicals:	28 percent
Perfumes and flavorings:	11 percent
Diagnostics:	10 percent
Instruments:	7 percent
Plant protection:	3 percent
Others:	1 percent

Human health care represents the bulk of Roche's business, and two of its past products, the tranquilizers Valium and Librium, have been among the most successful drugs ever sold. The single largest market is North America with 40 percent of sales (14).

Biotechnology at Roche has had an unusually controversial history involving four separate organizations: Roche USA, the Institute of Molecular Biology (Nutley, New Jersey), the Basel Institute of Immunology, and Roche corporate headquarters in Basel. During World War II, in fear of German occupation, Roche top management (including its president) and much of its financial structure and resources, were moved to the U.S. At the end of the war, top management returned to Basel, but over the years, the American company had acquired a semi-autonomous status. With the opening of the Institute of Molecular Biology in 1968, the U.S. also acquired its own private basic research institute specializing in the new technologies associated with genetic engineering and gene expression. On the Swiss side, the Basel Institute of Immunology opened in 1969. Both research institutes rapidly developed a solid reputation in molecular genetics, mammalian cell gene expression, and protein chemistry (at Nutley) and immunology (Basel). However, technology transfer to the corporate side did not immediately follow. This raised several questions:

1. How important was biotechnology to the company?

2. If it was important how could technology transfer be carried out?

3. Should the new technologies be introduced only in Basel? or only in Nutley? or in both?

Though not totally convinced of the impact of biotechnology on future profits, Roche could not afford to ignore it. The chosen mechanisms were to transfer groups from the Institutes into corporate R&D, establish biotechnology units, and recruit new staff in both Nutley and Basel. Roche was also one of the first major pharmaceutical companies to enter into an agreement with a new biotechnology company (Genentech and alpha-interferon). The American management pushed for an aggressive policy with a key role reserved for Nutley. The integration of these separate organizations into a smoothly operating entity still remains to be done.

During the past 2 years, there have been major management changes in Basel involving the departure of the heads of the Biotechnology Unit and of the Applied Immunology Groups, as well as the stepping down of the present head of R&D. It is felt that these changes have been due, in part, to the controversies over biotechnology policy (what, how much, where).

The Biotechnology Unit in Basel has a staff of 95, of which some 40 are Ph.D.'s (16). Its main activities are in peptide chemistry, genetic engineering, and immunomodulators (particularly focusing on interferon and IL-2). An area more closely related to its traditional markets are projects dealing with alternative methods for synthesizing vitamins and the manner in which vitamins are metabolized in the human body. Finally, Roche has been very successful in developing a malaria vaccine that is currently being tested.

Roche seems to have fewer agreements with other biotechnology companies. This is probably due in large part to its substantial financial and manpower commitments to its own research institutes and corporate R&D.

SANDOZ is the third largest of the Swiss pharmaceutical/chemical companies with a 1985 annual sales of SwF 8.5 billion ($3.46 billion) and profits of SwF 529 million ($215 million) (17). Like Roche and Ciba-Geigy, Sandoz has a diversified business that includes pharmaceuticals, agricultural products, foods, dyes, and seeds. Of these, pharmaceuticals (46 percent of sales), chemicals (25 percent), and agricultural chemicals (7 percent) represent the three largest sectors (17).

Research at Sandoz is decentralized. Its research institute in Vienna has an annual budget of approximately $50 million and a staff of 400, of which 80 are scientists (18). The main focus at the institute has changed over the years. It was initially antibiotics, then parasitic diseases, and more recently a combination that includes infectious disease, immune mediators, proteases, and new approaches to cancer therapy. In addition to Vienna, there are major research centers in Basel and Hanover, New Jersey. Sandoz's Austrian subsidiary, Biochemie Kundl, manufactures antibiotics and has a facility for research in downstream processing.

In Basel, the research staff numbers around 100, and is divided into four groups whose activities are (18):

(1) DNA technology: cloning and production of immunomodulators and endocrine products;

(2) Cell biology: gene transfer techniques and gene expression;

(3) Microbiology: screening of new strains for antibiotic production; and

(4) Bioprocessing: efforts are divided into biological response modifiers and microbial fermentation.

Apparently, activities in the agricultural sector are primarily associated with their two American acquisitions: Northrop King and Zoecon. The number of external agreements is fairly limited. As in the case of the two other major

companies, Sandoz seems to be trying to integrate the new technologies into their traditional research structure.

BIOGEN was established in 1978, and though it is an international company with operations in Cambridge, Massachusetts, and Geneva, Switzerland, it was originally perceived as a European start-up with serious involvement of key European scientists. Its staff numbers 360 (230 with 25 Ph.D.'s in Cambridge and 130 with 21 Ph.D.'s in Geneva) (19). Both Cambridge and Geneva are active in research, production, medical testing, and marketing. However, process development only takes place in the U.S. Biogen also maintains laboratories in Geneva, Ghent and Zurich (related to activities of some of the members of the Scientific Board). Its 1985 income (primarily from R&D contracts and interest) was $21.45 million, with a net loss of $19.1 million (20).

Like Genentech in the U.S., Biogen's objective is to become a fully integrated pharmaceutical company, and is constructing a 43,000 square meter production facility in Geneva. Their first product (licensed to Schering-Plough) is alpha interferon, which seems to show positive results on bladder cancer, hairy cell leukemia, and venereal warts. Biogen acquired 50 percent of the German company Bioferon in order to better market gamma interferon in the EEC. Their IL-2 and hepatitis vaccine are being licensed out.

Biogen's research is organized into groups working on: cell biology, microbiology, molecular biology, peptide synthesis, and oligonucleotide synthesis. Their research and product development strategy is to study the inhibition of natural immunomodulators such as IL-2. The inhibitors are of three classes: receptors, natural products, and IL-2 analogs. The same approach is being pursued for IL-1 and IL-3. In addition to alpha interferon, there is similar research being conducted on gamma and beta-interferons. In vaccine production, they are concentrating on a hepatitis-B vaccine. Outside of human health care, they are pursuing projects for the agro-food market: animal growth hormones (swine, bovine and insulin-like growth factors) and characterization of a herbicide from Streptomyces.

As with many of the American start-ups, Biogen has an excellent record of scientific accomplishments and an ambitious portfolio of R&D projects. It has been plagued with management problems and the need to move towards profitability. These problems are compounded by the awkward two-facility operation. The original rationale for this corporate structure was the recruitment of American scientists who would not relocate to Europe. Now, the persistent rumor is that corporate headquarters in Cambridge may decide that the Geneva facility does not justify its cost, and will choose to consolidate its operations into the U.S.

INDUSTRIAL OVERVIEW

The characteristics of the four companies studied here are summarized on Table 4. It must be noted that while there is a uniformity of opinion among the Swiss "Big Three," this does not necessarily apply to Biogen, which has an unusual role as an international start-up. The views of corporate managers and scientists are summarized below:

Table 4.

CHARACTERISTICS OF COMPANIES VISITED

	Ciba-Geigy	Hoffmann-La Roche	Sandoz	Biogen
Annual Sales 1985 in millions of $ (SwF) % increase	7,407 (18,200) 4%	3,622 (8,900) 8%	3,460 (8,500)	21.4 -32%
Net Profit 1985 in millions of $ (SwF) % increase	598 (1,470) 23.5%	184 (452) 19%	215 (529) 14%	-19.1 -45%
Business Sectors	Dyestuffs & chemicals Pharmaceuticals Agricultural Agricultural Plastics & additives Ilford Electronic equipment	Pharmaceuticals Vitamins & fine chemicals Perfumes & flavorings Diagnostics Instruments Plant protection	Pharmaceuticals Chemicals Agricultural chemicals Dyes Foods Seeds	Contract R&D Licensing Pharmaceuticals Animal Health Care
R&D Expenditures in millions of $ (SwF) % of sales	593 (1,456) 8%	500 (1,246) 14%	N/A	31 144.8%
Areas of R&D	New drugs: alpha-IF TPA, ILGF Protease inhibitors Tissue culture for secondary metabolites Animal health care Plant biology	Peptide chemistry Genetic engineering Immunomodulators Biological synthesis of vitamins Malaria vaccine	Immunomodulators & endocrine products Gene transfer techniques New strains for antibiotic production Bioprocessing	Inhibition of immunomodulators Research on alpha, beta, & gamma interferons Hepatitis B vaccine Animal growth hormones

There is a general consensus that the universities should carry out basic research and educate scientists. Industrial support is crucial since cantonal financing plays such an important role. Though informal relationships between academic scientists and industry are excellent, there are few formal arrangements and no mechanisms for technology transfer. In the case of Biogen, it is important that it can tap academic resources and it does so by funding professorships and laboratories (e.g. in Edinburgh, Ghent and Zurich).

The "Big Three" have a decentralized mode of research, combining corporate R&D with basic research institutes. Approximately 40 percent of this research is carried out abroad (much of it in the U.S.) (21). There is still a great deal of uncertainty and debate about how biotechnology will affect the Swiss pharmaceutical/chemical industry. The corporate R&D strategies are conservative and focus on product-related areas (except in diagnostics, biotechnology is still a poor source of new products). In principle, the basic research institutes should provide a mechanism for both high risk exploratory research and technology transfer. In practice, as previous sections have indicated, that has not been the case. Two key problems have yet to be resolved: (1) Should such an institute be focused on a specific research program (e.g. immunology) or should it be wide ranging? (2) How do you develop technology transfer from the institutes to corporate research groups? Though they prefer to concentrate their efforts in-house, the strong financial status of these corporations allows them to enter into agreements with other companies, including new biotechnology companies, to acquire those technologies and products that they need. As in the case of Biogen, these new biotechnology companies maintain an extremely aggressive research policy, very often on the basis of R&D contracts and/or joint ventures with larger companies.

There is strong industrial opposition to any federal government intervention in business. This was evidenced by the recent defeat of a government initiative to create a SwF 100 million ($40.7 million) (4) fund to guarantee venture capital investments. Though not essential to its growth, Biogen will accept certain kinds of government support. Realistically, this is more likely to come from cantonal government in the form of tax credits, real estate arrangements and work permits for foreigners.

It is generally felt that the growth of biotechnology in Switzerland will take place in the large companies. The creation of new companies is viewed as improbable and there is little interest in attracting U.S. biotechnology companies.

The main objective of the companies is to maintain an open business environment in Switzerland. The biggest fear is that tight environmental regulations would block the introduction of new products. Industry mobilized a highly vocal opposition to an initiative that would have effectively prevented further animal experiments. Switzerland is also faced with the dilemma that it is almost totally dependent on foreign markets, but does not belong to the EEC. Therefore, there is strong concern that government measures in the EEC, Japan and the U.S. could affect their operations.

VI. CONCLUSION

How does Switzerland compare with its European neighbors, the U.S. and Japan? The answer to this question lies as much in what has not happened as in what has happened. Ten years ago, at the beginning of the biotechnology era, Switzerland was in a highly advantageous position. It had four major university centers with excellent research groups and good students. In addition, there were industry-funded research institutes both in Switzerland and abroad. The industrial sector had three world-class multinationals in pharmaceuticals/chemicals and one in food processing. The situation today has not changed much, except for the creation of Biogen, properly speaking not a Swiss company. In contrast, the many other countries entering the biotechnology race have moved aggressively to place themselves in more favorable positions.

Switzerland is conservative, decentralized, and decision-making is by consensus. The role of the federal government has not changed much. Its clearest function is the funding and coordination of basic research and university education. The SNF is a model of its class and is well respected both in Switzerland and abroad. It has refrained from promoting research areas or identifying topics that may prove to be of industrial interest. The function of the Federal Office of Science and Education is even more limited, coordinating federal policies and serving as a source of information for initiatives and legislation by the government. A very small number of our contacts were critical of the BBW and believe that it should have taken a leadership role in developing a biotechnology program. However, even if a more aggressive leadership is forthcoming, it appears unlikely that there is a consensus for change in the policies of the BBW.

Insofar as government initiatives are concerned, it may very well be that the most important ones are at the cantonal level. The main candidate would be the canton of Basel with its university, two research institutes, three pharmaceutical companies, and a number of banking and financial institutions. There is great interest in regional high technology development involving Basel, Strasbourg (in France) and Stuttgart (in FRG). Preliminary discussions are now under way, but it is too early to predict what may happen.

At the research level, the Department of Molecular Biology at Geneva is no longer the major research center it once was. Though the departments of Molecular Biology I and II and the Institute of Biotechnology in Zurich continue to do quality research, cooperation between these various groups is considered to be fairly minimal. In none of these institutions, the Biozentrum in Basel included, is there any significant technology transfer to industry nor are there any major plans to do so.

In industry, the attitude towards biotechnology and its impact on the major sectors of pharmaceuticals and agricultural chemicals has been ambiguous and conservative. Management decisions have been unusually controversial and probably resulted in major changes of personnel at the top. Of the three major corporations, Ciba-Geigy seems to have developed the best overall strategy though its difficulties with the FMI are still far from over, and it still remains to be seen how the FMI (under new direction) will interact with

the agricultural center in North Carolina and Swiss corporate R&D. It will also be interesting to see whether contracts, joint ventures and acquisitions of U.S. companies continue to increase in the near future. As for Roche, management reorganization may better integrate biotechnology into its corporate structure. Of the three, Sandoz seems to have made the smallest commitment to these new research directions. As expected, Biogen is in a different category, and the question remains whether their present Cambridge-Geneva axis is operationally and financially practical. The single largest issue for all of these companies is that U.S. sales and profits are of major importance. At the same time, R&D carried out in the U.S., though more expensive, can draw on the largest scientific manpower pool in the world, plus attract scientists from elsewhere. This argues for basing a significant proportion of their activities in the U.S.

There is no evidence of any major effort to launch new companies in biotechnology. The defeat of the government initiative for a fund to guarantee risk capital investments is indicative that the environment for such activities does not exist at the present time. Neither have any U.S. companies established themselves in Switzerland nor shown much interest in such prospects. This is readily understandable given the high cost structure. difficulties in setting up a Swiss company and in obtaining work permits for foreign staff, the lack of government incentives, and the fact that Switzerland is not in the EEC.

The Swiss situation is stable and there is little motivation for change given the strong economic performance of the past 2 years. Nonetheless, many of my contacts were concerned over the long-term situation. Many are keenly aware of the serious difficulties experienced earlier in the electronics and watch industries. Given the research base, the industrial capacity, the pool of scientists (both Swiss and foreign), the financial resources, and the cooperative attitude of the government, it would be foolhardy to discount a strong position for the Swiss biotechnology industries in the future. However, this is unlikely to occur without major changes in the relationships between research organizations, companies, and both cantonal and federal authorities.

ACKNOWLEDGMENTS

Dan Harris. Commercial Specialist, Foreign Commercial Service, American Embassy, Bern

REFERENCES

1. Fiechter, A., Director of the Institute of Biotechnology, Swiss Federal Polytechnic Institute, Zurich, Switzerland, personal communication, March 11, 1986.

2. Wissenschaftspolitik, Nr. 2/1985, July 14, Bern.

3. Garke, Esther, "Higher Education in Switzerland", UNESCO, 1981.

4. Hochstrasser, U., Director & Roulet, N., Deputy Director, Federal Department for Education and Science, Switzerland, personal communication, March 12, 1986.

5. Schweizerischer Nationalfonds zur Forderung der wissenschaftlichen Forschung, Jahresbericht 1984, Wildhaingweg 20, 3001 Bern.

6. Arber, W., Rector, Biozentrum, Basel, Switzerland, personal communication, March 12, 1986.

7. Basel Institute for Immunology, Annual Report, 1984.

8. Heusler, Karl, Acting Director of Friedrich Miescher Institute, personal communication, October 10, 1985.

9. Stingelin, V., Director of Business Development, Battelle Institute, Geneva, Switzerland, personal communication, March 17, 1986.

10. The International 500, Fortune, August 19, 1985, pg. 184.

11. Ciba-Geigy, Annual Report 1985.

12. Burk, Robert, Special Assistant to the Director, Biotechnology Department, Ciba-Geigy, personal communication, March 14, 1986.

13. Financial Times, London, November 23, 1985.

14. Financial Times, London, March 25, 1986.

15. Financial Times, London, January 22, 1986.

16. Gillessen, D., Director of the Biotechnology Research Unit, & Herzog, E., Vice Director of the Central Research Unit, Hoffmann-La Roche, personal communication, October 10, 1985.

17. Financial Times, London, March 21, 1986.

18. Einsele, A., Biochemical Engineer, & Bachmayer, H., Director of Sandoz Research Institute, Vienna, personal communication, October 10, 1985.

19. Sautelle-Smith, B., Managing Director; Buchanan, Iain, Director of Marketing for Europe; Rouiller, M., Manager of Regulatory Affairs; Galazka, A., Director of Clinical Research; Favre, D., Public Relations; & Allet, B., Head of R&D, Biogen, personal communication, March 17, 1986.

20 Biogen, Annual Report, 1985.

21. The Swiss Chemical Industry in Figures, Swiss Society of Chemical Industries, 1985.

APPENDIX

Individuals and Organizations Visited

Government

Federal Department for Education and Science: Dr. U. Hochstrasser, Director; Dr. N. Roulet, Deputy

Universities and Research Institutes

Biozentrum of the University of Basel: Professor Werner Arber, Rector of the University and Professor of Microbiology; Dr. Thomas Bickle, Professor; Dr. C. Brack, Research Associate

Institute of Biotechnology, Federal Institute of Technology - Zurich: Professor A. Fiechter, Director; Dr. I. Adler, researcher in the pilot plant.

Institute of Microbiology, University of Geneva: Professor Bernard Mach, Director

Friedrich Miescher Institute: Dr. Thomas Hohn, group leader

Battelle Research Institute - Geneva: Dr. V. Stingelin, Director of Business Development; Dr. J. Sambeth, Head of the Biotechnology Unit; Dr. F. Dawson, Institute Director

Companies

Hoffmann-La Roche: Dr. Dieter Gillessen, Acting Director of the Biotechnology Research Unit; Dr. Ernst Herzog, Vice-Director of the Central Research Unit

Ciba-Geigy: Dr. Karl Heusler, Director, also Acting Director of the Friedrich Miescher Institute; Dr. Robert Burk, Special Assistant to the Director of the Biotechnology Department

Sandoz: Dr. Arthur Einsele, Biochemical Engineer from the Pharmaceutical Division, Pharmaceutical Division; Dr. Helmut Bachmayer, Director of the Sandoz Research Institute in Vienna

Biogen: Mr. B. Sautelle-Smith, Managing Director; Mr. Iain Buchanan, Director of Marketing for Europe; Dr. M. Rouiller, Manager of Regulatory Affairs; Dr. A. Galazka, Director of Clinical Research; Mr. D. Favre, Public Relations; Dr. B. Allet, Head of R&D

SECTION I

BIOTECHNOLOGY IN THE UNITED KINGDOM

SUMMARY

The United Kingdom is one of the principal countries involved in biological research and its potential application to industry. Its greatest strengths have been the excellence of its research institutions and centers of higher education. The British research establishment has often been criticized for its poor record in commercializing its scientific findings.

Biotechnology has been recognized by the British government as one of the strategic sectors for future industrial growth. Though there is no national plan for biotechnology, the Thatcher government has taken a number of measures to increase the cost-effectiveness of basic research, promote technology transfer and industrial R&D and stimulate the establishment of small, new biotechnology companies. This has been done during a period of stringent budget cuts and with little evidence of a long-term, concerted effort.

Government policies have come under severe criticism. There is growing concern at all levels that the science base is being eroded, and that the uncertain economic situation coupled with the traditional conservatism of British management prevents British industry from taking full advantage of the research from British laboratories. Though university-industry interactions have improved, and a significant number of small, new biotechnology companies have been created, it is uncertain whether the U.K. will be able to be scientifically and industrially competitive in numerous areas. One likely outcome is an increase in international collaboration with foreign laboratories and companies. Given the present anti-American political climate, it remains to be seen whether the British government will lean towards agreements with U.S. companies or those within the EEC.

I. INTRODUCTION

The U.S. and the U.K. enjoy a special relationship based on a common history and close political and commercial ties. To a greater degree than its European neighbors, the U.K. has been going through the painful shift away from traditional manufacturing to service and high technology industries. The conservative government of Mrs. Thatcher has pursued a policy of tight money, decreased government spending and privatization of state-owned industries.

The predicted growth rate for 1986 is 2.5 percent, which probably marks a slowing down of the economy following a long period of steady, moderate expansion with an expected inflation rate of 5 percent. The U.K. has paid a price for this economic policy with one of the highest unemployment rates in Western Europe (13 percent) (1).

The British government is trying to create a favorable, non-inflationary environment in which private industry can flourish. One important aspect of government policy is to make more effective industrial use of the research and skilled manpower of Britain's universities and research laboratories. Biotechnology has been selected as one of the strategic sectors for improved

0205

technology transfer. The U.K. starts out with certain significant advantages. Its laboratories have been in the forefront of biological research with historical achievements, which include the elucidation of the structure of DNA, the development of bacterial genetics, and the generation of techniques for protein and DNA sequencing and for the production of monoclonal antibodies. Their research has maintained a level of excellence in most important biological subjects. Traditionally, U.K. laboratories have maintained close ties to their U.S. counterparts. The U.K. also has a small number of technically advanced and commercially successful chemical and pharmaceutical multinationals, plus the largest collection of small, new biotechnology companies outside the U.S. Last, but not least, it is a major center for venture capital and for scientific and commercial information. It remains to be seen whether the appropriate mechanisms exist to exploit these assets.

[In order to evaluate the present state of biotechnology in the U.K., 37 meetings were held with key U.K. scientists, government officials, and industrial managers.]

II. GOVERNMENT POLICY

The British government does not have a ministry for science and technology. Science policy and funding are based on Lord Rothschild's principle of "customer-contractor," with research programs associated with individual government departments.

Basic research in the U.K. is funded through the University Grants Committee (UGC) and the Research Councils, both under the Department of Education and Science. Figure 1 summarizes the principal organizations involved in biotechnology. The UGC gives block grants to each university to cover both educational and research expenses. The amounts allocated to each activity varies from institution to institution and are not known (though as a rule of thumb, one-third of the time of the faculty should be spent in research). Policy for research councils is formulated by the Advisory Board for the Research Councils (ABRC). Industrial innovation is the responsibility of the Department of Trade and Industry through its Biotechnology Unit and the British Technology Group.

The Conservative government has been committed to reduction of government expenditures, privatization of state enterprises, and decentralization of government activities. In the specific area of science policy, the government has acted to:

(1) maintain a constant science budget while defining priorities and a strategy for implementation;

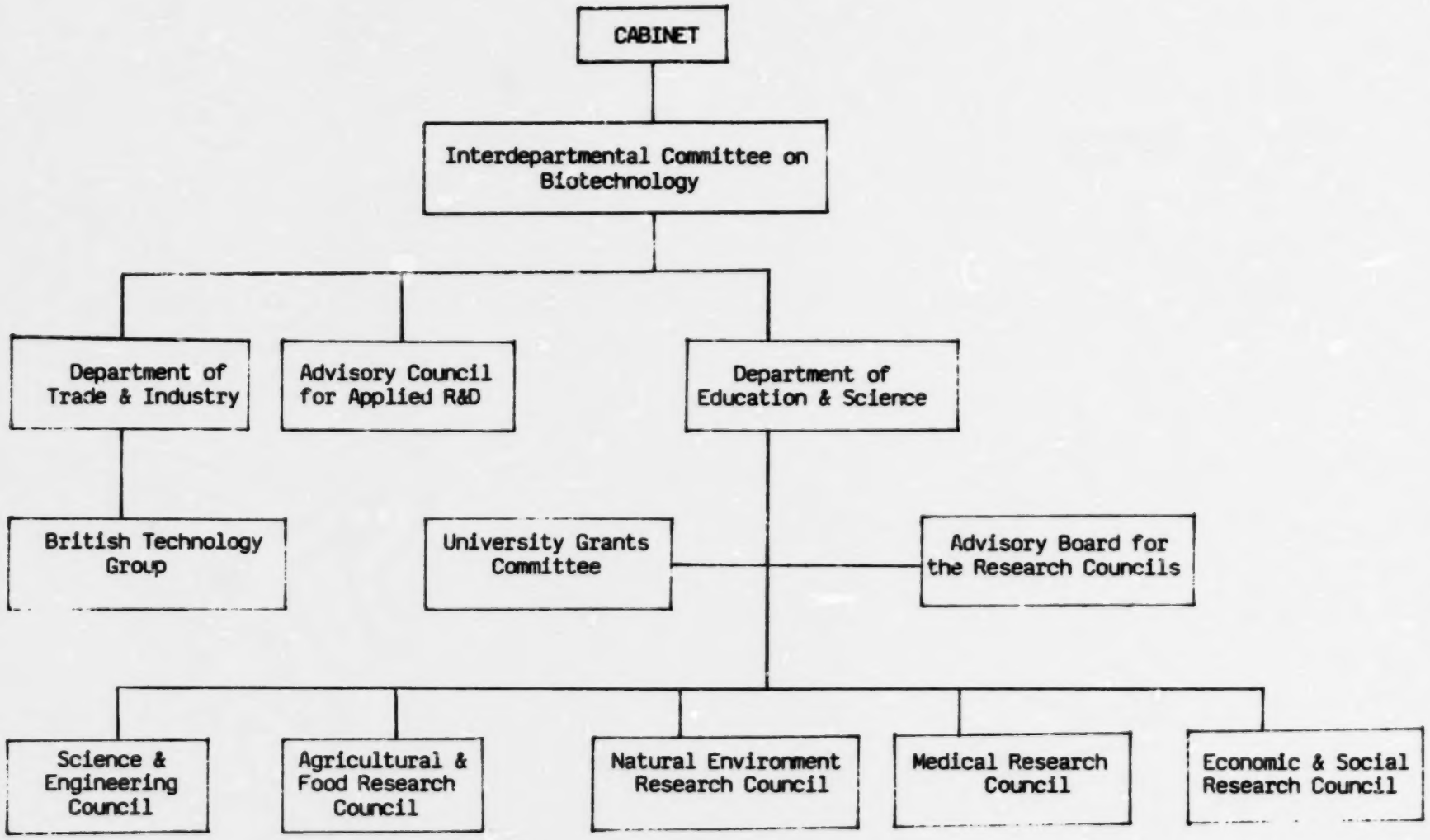
(2) reduce university expenditures;

(3) increase technology transfer to the industrial sector; and

(4) increase industrial innovation and create new companies to generate economic growth.

0206

Figure 1.


CABINET
Interdepartmental Committee on Biotechnology
Department of Trade & Industry
Advisory Council for Applied R&D
Department of Education & Science
British Technology Group
University Grants Committee
Advisory Board for the Research Councils
Science & Engineering Council
Agricultural & Food Research Council
Natural Environment Research Council
Medical Research Council
Economic & Social Research Council

BEST COPY AVAILABLE

Biotechnology is one of the strategic sectors identified by the government and has been used as a testing ground for many policies. There are, however, serious contradictions in government policy that raise doubts as to its ultimate success.

Medical Research Council (MRC): The objective of the MRC is to conduct work that will improve human health. The MRC has two large institutes (National Institute for Medical Research and the Clinical Research Center) and 56 research units, many attached to universities (2). It has a staff of 1,000 scientists and funds 1,500 more at universities. The budgets for these institutes accounts for 60 percent of the annual MRC budget (see Table 1), while the remainder is spent in university research and educational programs (3). The MRC laboratories, and its grantees, have been responsible for some of the seminal work in modern biology and many continue to do so.

Using a liberal definition of biotechnology, the MRC spends £27 million ($35 million)* on biotechnology research, making it the largest funding agency in this field (3). Though the total MRC budget has increased from £101.7 million ($131.8 million) in 1981-82 to £121.6 million ($157.6 million) in 1985-86, this represents an actual reduction of 1.4 percent when corrected for inflation. Non-research costs, such as salary increases above government guidelines, increases in pensions, and increases in contributions to international efforts have resulted in an overall decline of 4 percent during this period. This has led to a decrease in the number of funded grants (440 in 1984-85 versus 495 in 1981-82) and Ph.D. studentships (160 in 1984-85 versus 273 in 1981-82) (4).

The MRC is organized into divisions that come under the supervision of the following boards: Neurobiology and Mental Health Board; Cell Biology and Disorders Board; Physiological Systems and Disorders Board; and Tropical Medicine Research Board. Most of the biotechnology-related research comes under the Cell Biology and Disorders Board.

In order to improve technology transfer, the MRC has taken the following measures (3):

(1) Industrial studentships: MRC pays the stipend and a £600 ($777.80) laboratory fee for the student to complete his thesis project in industry.

(2) Cooperative awards: Joint university-industry projects have their cost shared on an equal basis between the MRC and industry [average amount: £60-70,000/year ($78-$91,000)].

(3) Collaborative research center: Built near Mill Hill, it provides laboratories for applied projects in collaboration with industry.

*Average exchange rate for 1985: Pound sterling (£1) = $1.2963.

Table 1.
R&D Budgets of Government Agencies
Involved in Biotechnology

Agency	1985/86 Budget* Total	Biotechnology
Department of Trade & Industry	£389.9M ($505.4M)	£4M ($5.2M)
Agriculture & Food Research Council	£49.7M ($64.4M)	£18M ($23.3M)
Economic & Social Research Council	£18.8M ($24.4M)	---
Medical Research Council	£121.6M ($157.6M)	£27M ($35M)
Natural Environment Research Council	£64.7M ($83.9M)	---
Science & Engineering Research Council	£286.8M ($371.8M)	£4M ($5.2M)**
University Grants Committee	£581.0M ($753.2M)	Not known

M = millions
*Average exchange rate for 1985: £1=$1.2963.

**An additional £16.5M ($21.4M) are spent in basic research in biology.

SOURCE: Annual Review of Government Funded R&D, 1985.

The dilemma that faces the MRC today, is whether to protect as best as possible the research in basic and clinical science or redirect some of its diminishing resources towards industrial applications.

Agricultural and Food Research Council (AFRC): Its primary objective is to increase scientific knowledge in areas related to agriculture, horticulture and food. Besides its budget of £49.7 million ($64.4 million), it receives an additional £51.8 million ($67.1 million) from the Ministry of Agriculture, Fisheries and Food (5). It operates 20 institutes in England and Wales, and 2 in Scotland. Sixty percent of the budget is spent on the AFRC institutes, with the remainder going to universities. Some £18 million ($23.3 million) is spent on biotechnology. In addition, AFRC institutes receive some £1 million ($1.3 million) in contracts from the EEC (6). Fifteen U.S. companies and three non-profit organizations have contributed £519,000 ($673,000) to the AFRC, primarily to finance projects at some of its institutes (5).

Of the research councils supporting biotechnology R&D, the AFRC is the one facing the most severe budget cuts and undergoing the most extensive restructuring. The AFRC will have an overall budget reduction of 20 percent during the period 1981-90. Contributions from the Ministry of Agriculture will be reduced by 5 percent in 1987, and by 5 percent in 1988. There have been staff reductions of 600 in 1985, 600 in 1986, and a further 600 are projected for 1987. The reorganization has the objective of moving away from agricultural support and into agro-food research with a strong emphasis on biotechnology, and will be implemented by (6):

(1) consolidation into 8 research institutes,

(2) increased research at universities [from £4.8 million ($6.2 million) to £6.4 million ($8.3 million) in 1984-85], and

(3) increased technology transfer and external funding through the Agricultural Genetics Company (AGC) and other companies. AFRC also funds cooperative research groups at universities in collaboration with industry.

One of the more controversial decisions of the government involves the planned privatization of the state-owned National Seed Development Organization (NSDO) and part of the AFRC's Plant Breeding Institute (PBI). The PBI is composed of a plant breeding division (to be sold) and a basic research division. Eighty percent of the income of the NSDO [£2.9 million ($3.75 million) in profits and £1.75 million ($2.27 million) in dividends] comes from the production and sales of seed varieties developed by the PBI (7). This income is considered sufficient to cover the costs of PBI's plant breeding operation. The potential buyers include several major multinationals, such as ICI, Royal Dutch Shell, and Ciba-Geigy. Opposition to the sale is based on:

(1) dissolution of an integrated organization that includes everything from molecular biology to production and marketing of new plant varieties,

(2) farmers' belief that their own best interest is served by having PBI and NSDO remain in the public sector, and

(3) concern that they will go under foreign ownership.

Science and Engineering Research Council (SERC): Its objective is to maintain and enhance the research capabilities of U.K. universities in all areas of pure and applied science and engineering (except those funded by the AFRC, MRC and NERC). The SERC does not maintain its own laboratories and carries out most of its research at universities. Four boards are responsible for the activities of the SERC: the Engineering Board, the Nuclear Physics Board, the Astronomy, Space and Radio Board, and the Science Board. Special directorates have been established (e.g., Biotechnology) to fund and coordinate the activities of academic and industrial researchers in projects of economic relevance. The Biotechnology Directorate is composed of equal numbers of research scientists and industrialists. It has defined a number of priority sectors (8):

- o Biocatalysis, including immobilized cells and enzymes,
- o Plant genetics and biochemistry,
- o Large-scale growth of mammalian and plant cells,
- o Fermentation technology,
- o New downstream processing technologies, and
- o Sensors and bioelectronics.

The directorate has pioneered in developing a number of technology transfer schemes (8):

(1) Cooperative research projects: the cost is equally shared between the government and industry.

(2) Training companies: arrangement between a company and an academic laboratory to solve a research problem and train graduate students.

(3) Cooperative Awards in Science and Engineering (CASE): funds students working on projects in collaboration with industry.

(4) Research clubs: brings together academic laboratories and companies working on a specific research sector. For example, the Protein Engineering Club brings together six universities (Bristol, Leeds, Oxford, Sheffield, Birbeck, and Imperial) and five companies (Celltech, Glaxo, ICI, RTZ, and E. Sturgis) The companies contribute £30,000 ($38,800) each over 4 years and SERC £2.5 million ($3.24 million) over 4 years. In addition, the Biological Sciences Committee will fund £900,000 of basic research projects related to protein engineering (9). Other clubs being formed are in membranes, animal cell physiology and antibiotics.

(5) Round tables: periodic, open discussions between scientists and industrialists on specific research topics.

The Biotechnology Directorate was originally established for a period of 3 years, and its operations have been extended for a further 3-year period. This has been in spite of heavy opposition from scientists who do not believe that it is the function of SERC to support directed research.

SERC's budget has been maintained in real terms during the past few years, as has the budget of the Biotechnology Directorate. Nevertheless, its funding for biotechnology remains modest by international standards.

University Grants Committee (UGC): The purpose of the UGC is to fund research and teaching at the universities. In science, UGC funds are intended to provide a basic level of research and requires supplementary support from external sources (this is otherwise known as the dual support system). Since it is extremely difficult to differentiate between teaching and research functions, the budget figure that appears in Table 1 is based on theoretical calculations. UGC funding has been severely affected by cuts in government spending, declining by about 8 percent since 1981-82 and is likely to decrease at the rate of 1.5-2 percent a year in real terms (4). There are indications that a significant proportion of the cuts have been in research. Under severe political pressure, the government may provide an additional £145 million ($187.96 million) over the next 3 years [£35 million ($45.4 million) in 1987-88, £50 million ($64.8 million) in 1988-89 and £60 million ($77.78 million) in 1989-90] (10). It has also proposed to increase from £7 million ($9.07 million) to £10 million ($12.9 million) per year the allocation for new research equipment in specified universities (11). There would also be a supplement of £45 million for the period between 1986-87 to 1988-89 for the research councils (11).

Biotechnology Unit, Department of Trade and Industry (DTI): The DTI has been designated as the lead agency in biotechnology with the responsibility of developing and promoting industrial activities in this sector. Within the DTI there are four Industrial Research Establishments, one of which is the Laboratory of the Government Chemist. Charged with providing analytical and advisory services in chemistry, the Government Chemist, Mr. Ronald Coleman, was instrumental in setting up a cabinet-level Interdepartmental Committee on Biotechnology that brings together senior officials from government Departments and Research Councils. In addition, he established a Biotechnology Unit in his Laboratory.

The Biotechnology Unit has a staff of four full-time professionals and four specialists on leave from industry. It has a budget of £16 million ($20.7 million) for 3 years and its current budget is £4 million ($5.2 million) (12). Its most important objectives are: to support industrial R&D, to build up the infrastructure of biotechnology (e.g., culture collections and information services) and to promote sectors of biotechnology important to the U.K. economy. The Unit has defined four priority areas (13): (1) enzyme production and utilization, (2) biosensors, (3) agro-food, and (4) biochemical engineering. The Unit has formal ties with the SERC Biotechnology Directorate, but its relationships with the MRC and AFRC are much looser. It is felt that at the operational level, the biotechnology efforts of the Unit and the Research Councils should be better integrated.

R&D projects are financed through DTI's Support for Innovation Program. In the case of a single firm, the maximum support is 25 percent. If there are two or more partners (some of which could be academic), this could increase to 50 percent. The government contribution is in the form of a grant, ranging from £100,000 ($129,600) to £5 million ($6.5 million), though smaller sums would be considered (14). The average grant is for £100,000 ($129.600) (13). Foreign firms and multinationals are eligible as long as they maintain R&D and production facilities in the U.K. The company has to invest its own money first and is then reimbursed by the DTI.

Though preference is given to projects in the priority sectors, DTI will fund any high quality proposals. The funds available have been in excess of the number of eligible proposals. It is believed that this is due to the weakening of the science base in the U.K., the poor tradition in industrial R&D and the financial weakness of many U.K. companies.

British Technology Group (BTG): The BTG is the result of the merger of the National Research Development Corporation with the National Enterprise Board. Its objective is to promote technology transfer from government and government-funded laboratories to the commercial sector. It is a public corporation originally funded by the government, but now under a mandate to become self-supporting. Its 5-year plan involves an investment of £50 million ($64.8 million) per year (15) in technology transfer and the annual turnover is £22.44 million ($29.08 million) (16). The contracts awarded for biotechnology is £4 million ($5.19 million) and its present investment in biotechnology-related companies is £10 million ($12.96 million) (15).

Originally, the BTG had first refusal rights on the results from all government-funded research, but this policy has been changed by the Thatcher government. BTG has three types of contracts (15):

(1) development contracts: to determine the commercial feasibility of a product or process.

(2) joint ventures: BTG will fund up to 50 percent of a project and will be repaid from sales in a two-stage process. In the first stage, it will recover its capital with interest. In the the second stage, it will obtain a profit as a percentage of sales for a limited period. The maximum support for a biotechnology project is £0.5 million ($0.65 million).

(3) agent: BTG will license a product or process to a company. Preference is given to a U.K. company, but if one is not forthcoming, the agreement can be with a foreign company. This open policy has allowed it to earn £150 million ($194.4 million) from the sales of cephalosporins and made pyrethrin insecticides their most important product at present (15).

In addition, BTG may act as a source of venture capital (see Industry section). If a company has received a 25 percent grant from DTI, it can apply for up to 50 percent of the balance from BTG. The main research areas targeted by the BTG are (16):

- o immunology, especially new vaccines and diagnostic tests based on monoclonal antibodies;

- o agro-food, especially new plant products and mechanisms of disease and pest control;

- o biological production of pharmaceuticals and specialty chemicals; and

- o industrial applications of enzymes.

Though the BTG has had some notable successes, it has also encountered some of the same difficulties as the DTI. These are a shortage of acceptable proposals, and insufficient interest from U.K. firms.

Impact of National Health Service (NHS) Policy

In April 1985, the British government introduced a limited list of drugs which can be prescribed under the National Health Service (NHS). The "delisting" of established products was regarded as a breach of trust by the pharmaceutical companies, and the result has been the review of U.K. operations by many U.S. firms.

There have been several closures and/or cuts by U.S. drug companies in both R&D activities and manufacturing in the U.K. A.H. Robins has sold a manufacturing plant, opened in September of 1984, to Glaxo for an undisclosed sum. Warner-Lambert has announced the closing of its English plant and is concentrating all manufacturing at its Welsh plant. Eli Lilly has stated that "any new manufacturing process will go to Europe, if the economics are equal." Pfizer has cancelled two production projects worth a total of £35 million ($45.4 million). Wyeth, a subsidiary of American Home Products, has cut numerous jobs at its various manufacturing sites in the U.K., and has cancelled planned R&D investments worth £30 million ($38.8 million) (17).

G.D. Searle is phasing out its drug research in the U.K. and their headquarters and clinical research facilities (Searle's largest outside of the U.S.) will be relocated (18).

Besides the limited drug list, the industry was unhappy with the basic level of remuneration allowed under the NHS. Recent cuts have reduced profits from approximately 25 percent to the present 15-17 percent. In June 1986, the government redefined the "target rates of return on historic capital" for the first time since the turn of the century. Should members of the Association of the British Pharmaceutical Industry accept the proposal, the profit limits will rise by 1.5 percent on October 1, 1986, and rise again by 2 percent on October 1, 1987. The government has also suggested that further increases should be directly linked to the returns on investment recorded by companies in the FT 500 index (19).

III. UNIVERSITIES AND RESEARCH INSTITUTES

The number of important research laboratories and institutes in the U.K. is sufficiently large that it required us to concentrate on those that are most likely to affect the development of biotechnology as well as those that represent experiments in technology transfer.

(a) Financial Support: The cuts in the government budget have affected research institutions in different ways. The most severely affected have been the universities and the AFRC institutes. The universities have seen reductions in their teaching and support staff and in funds for buildings and capital equipment. Most of the university groups visited were highly rated and had maintained their levels of grant funding from the Research Councils. However, the decline in the infrastructure of the universities had effectively reduced their operational budgets while increases in teaching responsibilities had a negative effect on time spent in research. The AFRC is being forced to close most of its institutes and eliminate whole categories of research activities at the remaining ones (e.g., plant breeding, research on sugar beets). While the MRC Laboratory of Molecular Biology is considered the "jewel in the crown" of British biological science, the lack of growth has meant that there are no job opportunities for young investigators, no possibilities to pursue new research directions and severe limitations in the purchase of capital equipment. One of the objectives of government policy has been to increase the extent of external funding, particularly from industry. This has been partially successful, particularly in the various university biocenters and in some of the AFRC research institutes. This external support did not compensate for the loss of government funding. It should be noted that the U.K. is the only country visited where government support of biotechnology-related research is decreasing significantly in real terms.

(b) Scientific Research: The number of first-class biological research laboratories in the U.K. is impressive. They also cover a broad spectrum of biological research topics. Tables 2 and 3 summarize the research activities in the university laboratories and research institutes visited. They range from x-ray crystallography and computer modeling through developmental biology to biochemical engineering. Laboratories such as the MRC Laboratory of Molecular Biology pioneered in the development of monoclonal antibodies and DNA, RNA and protein sequencing, while Edinburgh was one of the first to develop an efficient vector system.

It is important to remember that while certain research areas such as molecular genetics, immunology and protein engineering are vigorously studied by laboratories in a number of other countries, the same is not true of topics such as plant proteins, gene transfer and expression in plants, fermentation technology, downstream processing, and biosensors. All of the latter are of crucial importance in the industrial application of biotechnology. Though the impact of diminished funds was not observable, it was pointed out that experimental approaches very often had to be tailored to the resources available. This means that certain experiments have to be postponed or abandoned altogether.

Table 2.
University Research Centers Visited

	Biotechnology Center University of Cambridge	Biocentre Leicester University	Department of Molecular Biology University of Edinburgh	Centre for Biotechnology Imperial College of Science & Technology	Biochemical Engineering Group University College, London
Principal Research Themes	Downstream processing New chromatographic procedures Membrane technology Immobilized Enzymes Biosensors	Yeast DNA replication Yeast vectors Mechanism for protein secretion Gene expression in higher plants Biosensors	Recombinant DNA Development of vectors Control of gene expression in prokaryotes & eukaryotes Novel vaccines for hepatitis & malaria	Development of vectors for bacilli, thermophiles & plants X-ray crystallography Computer modeling Biosensors Microbial Physiology Lignocellulose utilization	Fermentation technology Immobilized enzymes & cells Isolation & purification procedures Production of amino acids & antibiotics Design of fermenters & bioreactors

Table 3.
Research Council Institutes Visited

	Laboratory of Molecular Biology (MRC)	Rothamsted Experimental Station (AFRC)	John Innes Institute (AFRC)	Plant Breeding Institute (AFRC)	Center for Applied Microbiology & Research (PHLS)
Principal Research Themes	DNA sequencing of viral genomes Chemical & structural studies of: -proteins -nucleic acids -membranes -muscle Protein engineering Structure of eukaryotic chromosomes & chromatin Developmental biology of: -nematodes -drosophila -dictyostelium Interferon & its receptors Antibody synthesis & expression	Plant tissue culture Development of plant vectors Gene expression in plants Storage proteins in cereals Soil microbiology & nitrogen & phosphate uptake Chemical & biological pesticides	Plant biochemistry - photosynthesis Control of gene expression in plants Genetics of antibiotic synthesis in streptomyces Nitrogen fixation in rhizobium Plant-pathogen interactions Plant viruses (CMV)	New cereal varieties, also potatoes & legumes Cytogenetics Genetics of storage proteins in cereals Tissue culture of potato, brassica & legumes Salt tolerance in wheat Plant viruses Genetics of plant disease resistance	New genetically engineered vaccines Genetic engineering Pilot plant fermentation Protein purification Therapeutic products (Asparaginase) Role of bacterium in gastrointestinal cancers

(c) University/Institute-Industry Interactions: Of the countries studied, including the U.S., the U.K. has experimented the most extensively with technology transfer. The mechanisms being used are:

(1) CASE studentships;

(2) Teaching companies;

(3) University biocenters: these are intended to pursue research of industrial relevance. The Leicester Biocenter has four industrial sponsors (John Brown, Dalgety Spillers, Gallagher, and Whitbread), and all four university biotechnology centers have important industrial contracts;

(4) Both DTI and BTG provide financial support for collaborative projects between companies and academic laboratories; and

(5) Celltech and AGC (Agricultural Genetics Company) are new biotechnology companies established by government initiative and have access to the research findings of the MRC and AFRC respectively.

Most of these arrangements are recent and are described in the preceding Government Policy section. It is too early to assess their effectiveness, but some results are already becoming apparent. Academic scientists have become more conscious about the potential applications of their work, and are more keen to collaborate with industry in order to obtain additional funds. It is, however, also felt that academic scientists often lack sophistication in assessing the technical difficulties of commercial development and the actual value of their products/processes. The major limiting factor is the frequently uncoordinated and overlapping efforts of the various institutions and the limited number of U.K. companies willing, or able, to make use of the new technology (see sections on DTI and BTG).

(d) Staffing: At the present time, there does not appear to be a shortage of scientists in any given specialty. In general, the tight job market has made it reasonably easy to staff laboratories. In specialties where there is strong industrial competition (e.g., biosensors, protein purification and chemistry) academic salaries make recruitment more difficult. The greater concern is that the present situation is resulting in a "brain drain." A study commissioned by SERC 4 years ago concluded that there was no shortage of biotechnology specialists. More recently, a number of observations [e.g., the number of university scientists under 35 years old is declining at a rate of 2 percent a year; in the Department of Virology, Glasgow University, out of 15 Ph.D.'s graduated since 1981, only 3 are still working in the U.K., while 10 have gone to the U.S. (4) have raised the issue again, forcing SERC to commission a second study which has not yet been completed.

Staffing problems are beginning to appear in the recruitment of senior scientific staff (i.e., institute directors, department chairmen) with international reputations since the salaries are not competitive with those paid in other countries and the work environment is deteriorating. This will

become more acute as young researchers go abroad, make their careers in foreign countries and stay away permanently.

The quality of many key U.K. laboratories has made them international centers and attracted first-class scientists from all over the world. They, in turn, contribute to the excellence of the science and make these laboratories way stations in the careers of many successful scientists. Decline in financial support of these laboratories will make them less attractive as international centers. As one research director said, "The Americans will be the first ones to stop coming. And they are like the Canadian geese, once they start migrating, can winter be far behind?"

(e) Education: Most of the scientists in the institutions visited were educated in universities. The selection process is fairly rigorous, particularly for the elite institutions such as Cambridge, Oxford and Edinburgh. A bachelor's degree in the biological sciences usually takes 4 years and the Ph.D. 3 years beyond that. The focus on the academic major and the good faculty-to-student ratio provides an excellent education.

IV. INDUSTRY

The U.K. has a number of well established pharmaceutical, chemical and food companies. The industrial scene is a highly volatile one, since the U.K. is also the only country besides the U.S. that has a large number of small, new biotechnology companies [estimated at 50, while the British Biotechnology Association numbers already 20]. These new firms have tried to establish niches in areas such as agriculture, waste treatment and biosensors. For the sake of simplicity, we have divided the U.K. companies into three categories: large, established corporations; government-initiated, new firms; and small, entrepreneurial, new companies. [Though Beecham is one of the major U.K. pharmaceutical companies, scheduling difficulties did not permit a visit and obtaining more detailed information.]

BEECHAM's principal activities have been in the area of prescription drugs, over-the-counter pharmaceutical products and consumer goods. Unlike other British multinationals, Beecham has experienced a serious decline in its U.S. sales primarily due to poor performance in cosmetics and fragrances. Its major strength is in R&D and production of antibiotics. In addition, it is producing vasodilators and vaccines against hay fever. It is not known how Beecham intends to apply the new biotechnology processes to its existing product line or to generate new ones.

GLAXO had its origin in the production of dried milk, and diversified successfully into penicillin and related antibiotics. It is one of the major U.K. pharmaceutical companies and Table 4 summarizes its activities. Glaxo's 1985 profits represent a 58 percent increase over 1984, and its overall earnings have increased sixfold over the past 5 years (21). This remarkable performance has been due to the success of its anti-ulcer drug, Zantac, which represents 41 percent of its sales (20).

Table 4.
Major Companies Visited

	Beecham	Glaxo	Imperial Chemical Industries (ICI)	Wellcome
Annual Sales 1985	£2.6bn* ($3.37bn)	£1.412bn ($1.83bn)	£10.7bn ($1.83bn)	£1.0bn ($1.2963bn)
Profits	£84.1M ($109.0M)	£266.7M ($345.7M)	£512M ($663.7M)	£44.9M** ($58.2M)
Business Sectors	Consumer products Pharmaceuticals	Anti-ulcerants Cephalosporins Bulk antibiotics Anti-hypertensive Respiratory products Veterinary Generics Foods & proprietary medicines	Petrochemicals & plastics Agriculture General chemicals Oil Colours, polyurethanes & specialty chemicals Fibers Paints Industrial explosives	Anti-herpes drugs Respiratory drugs Diagnostics Animal health care
R&D Budget	£86M ($111.48M)	£92M ($119.3M)	£299M (1984) ($387.6M) (1984)	£122M ($158.14M)
Areas of R&D	Penicillins	Anti-inflammatory Immunomodulators Anti-tumor agents Anti-hypertensive agents Analgesic agents Respiratory pharmacology	Single cell protein Biopolymers Plant breeding Plant pathogens Anti-cancer agents Mechanism of metastasis Beta blockers Antibiotics Immunology Enzyme engineering	Anti-viral drugs Anti-cancer agents Prostaglandins Immunomodulators
Activities in the U.S.	Acquisition of Norcliffe Thayer, proprietary medicine company	Acquisition of A.H.Robin's plant in U.K. New research facility at Triangle Park, N.C.	Acquisition of rest of of Garst Seed Co. Establishment of tissue culture & genetics research laboratory at Garst	

*Average exchange rate for 1985: £1=$1.2963. M=millions, b=billions
**An additional £23.8M ($30.85M) were distributed to the Wellcome Trust.
SOURCE: 1985 Annual Report of Accounts from each respective company.

Glaxo's impressive record has been based on the simultaneous launch of Zantac and its entry into the U.S. market. The sales of its U.S. subsidiary, Glaxo, Inc., went from $200 million in 1984 to $365 million in 1985 (an increase of 78 percent) and it now represents close to a third of group sales. Glaxo is also developing its Far East market which, while still small (7.5 percent), has increased by 44 percent from last year (21). This strategy has also resulted in the phasing-out of the food business, and a concentration on ethical drugs.

Glaxo Group Research is responsible for the R&D and has a worldwide staff of 2,000. Its estimated 1986 budget is £100 million ($129.63 million). There are two main research centers located in Greenford and in Ware, each with a staff of approximately 500 (20). The center at Greenford focuses on biotechnology, infectious diseases, immunology, cancer research and skin biology, while the center at Ware is responsible for research on alimentary, cardiovascular, respiratory, and central nervous systems; metabolic diseases and toxicology. It is estimated that £2 million ($2.59 million) are spent annually on biotechnology research, particularly on screening for new secondary metabolites, interleukins and renin inhibitors. In line with its expansion into the U.S. market, Glaxo is establishing a new basic research center in Triangle Park, North Carolina. This will initially have a staff of 40 and eventually grow to 200 (22). The program plan for this new center has not yet been decided, but it is likely to involve at least some aspects of cell biology.

The attitude of Glaxo towards the rapid pace of biological research and the new biotechnology methods has been cautious. The view is that biotechnology is simply an enabling technology to be exploited. It prefers to carry out almost all of its research in-house, and only the miniscule sum of £500,000 ($648,000) is spent on external contracts and university support (22). At the present time, Glaxo has a very large cash reserve that amounts to 40 percent of the group's assets, and it remains to be seen how this will be put to use (20).

IMPERIAL CHEMICAL INDUSTRIES (ICI) is one of the world's largest chemical groups, and the first U.K., non-oil company to generate £1 billion ($1.2963 billion) in profits (23). ICI's operations are global and its basic strategy is to use a large variety of different feedstocks for conversion into commercial products. Table 4 gives a summary of ICI's operations. ICI's biotechnology activities are in the Agricultural and Pharmaceutical Divisions. The Agriculture Division is responsible for 16 percent of sales and 20 percent of profits, while Pharmaceuticals, with only 7 percent of sales, generates 23 percent of profits (24). As in the case of many other U.K. multinationals, its American operations are responsible for a major proportion of group sales (30 percent) (25).

As sales of bulk chemicals, such as plastics, decrease and agrochemicals markets mature, ICI has made a major commitment to biotechnology and to developing markets for its new products. Spending on biological R&D is estimated at £96.6 million ($125.25 million) per year (26). ICI has established a new unit, the Biological Products Business, to exploit some of the new biotechnology processes. The major projects are:

(1) Pruteen animal feed and Myco-protein, for human consumption;
(2) Biopol, the new biological polymer; and
(3) CYCLEAR: treatment of cyanide wastes.

The Pruteen project was begun in 1968, with the objective of producing single cell protein for animal feed using methane from the North Sea. The microorganism Methylophilus methylotrophus was grown on methanol, the protein extracted, and converted into feed pellets. The project encountered many technical problems, not the least of which was the design of the 2 million-liter fermenter (23). The cost of the project was more than £80 million ($103.7 million) and took 12 years to complete (27). In the meantime, the cost of methane had increased while soybean prices had dropped. The plant has a capacity of 50,000 tons per year, but the product is not commercially competitive (23). The same technology has been used by ICI in a joint venture with the food company Rank Hovis McDougall. Fusarium is grown on hydrolyzed corn starch and converted into single cell protein and used for the production of Sainsbury's Savoury Pie, which has been successful in market trials.

The cyanide waste treatment was based on the isolation of a fungus that has a high level of cyanide hydratase, which converts cyanide into carbon dioxide and ammonia. Treatment tanks containing the enzyme can treat up to 100 gallons of waste per minute.

Biopol is a polymer of polyhydroxybutyrate produced by fermentation, and can be extracted to a purity of 92 percent. This seemed to be one of a promising new series of biological polymers, so ICI spun off a new biotechnology company, Marlborough Biopolymers, to exploit it. Though Biopol can be molded into a variety of different forms, and is biodegradeable at a slow rate, its price is not competitive given the drop in the price of oil and, consequently, other polymers.

ICI's R&D in the biological sciences is decentralized and the Agriculture, Pharmaceutical, and Crop Protection Divisions have their own research departments. In addition, there is a Corporate Biosciences Group which does research for the operating divisions as well as conducting its own long-term exploratory research. As the projects mature, they are transferred to the operating divisions.

ICI has followed an aggressive policy of identifying business areas and trying to integrate R&D, production, marketing and, when necessary, external contracts and corporate acquisitions. In the plant area, it has:

- transferred the plant biotechnology group from Corporate Biosciences to the Plant Protection Division, bringing with it projects on plant breeding for disease and pest resistance, development of multifunctional chemicals that will act as both pesticides and growth promoters, and biopesticides;

- purchased the remainder of Garth Seed Company, one of the largest U.S. producers of corn seed, with a total investment of £50-60 million ($64.8-$77.8 million) (28); and

- o invested £17 million ($22.04 million) in increasing its research capabilities in plant biology (28). This has been done three ways: (a) creating a genetics and tissue culture laboratory at Garth, (b) expanding the ICI laboratory at Jealott's Hill, U.K., and (c) the probable investment in plant research at Iowa State University in collaboration with the State of Iowa.

- o ICI is a potential purchaser of the Plant Breeding Institute when it is privatized.

ICI has been successful in pharmaceuticals with Nolvadex, an antiestrogen used in treatment of breast cancer following surgery. They are increasing their efforts in immunomodulators and lymphokines, human auto-immune diseases, and biology of metastasis.

Difficulties in staffing some of their new research groups will probably lead ICI to conduct an increasing proportion of their research in the U.S. The same is true of the newly established Diagnostics group.

ICI has been active in developing ties with academic laboratories in both the U.K. and the U.S. At the present time, it spends £3 million ($3.89 million) per year in the U.K., and a similar amount in the U.S. An example of a university-ICI agreement is that with Leicester University on molecular biology and genetics in areas consistent with ICI business interests. It is a 5-year program funded by ICI at the rate of £250,000 ($193,000) per year, with a staff of 12 including one or two ICI scientists (24).

WELLCOME

The Wellcome Foundation is a holding company that was wholly owned by the Wellcome Trust, a private charity. Twenty percent of the shares were sold to the public in February 1986, along with new shares to raise additional capital (29). Wellcome has done very well commercially, particularly in the U.S. which accounts for 45 percent of its sales and 73 percent of its profits (30). Zovirax, an anti-herpes drug, and Trocrium, a muscle relaxant, were extremely successful. The company maintains major research centers in the U.S. and the U.K. They have recently merged their animal health operations with ICI to create Coopers Animal Health.

Wellcome Biotech is an autonomous division of Wellcome. With a staff of 460, it is able to develop and license its own products (31). Research is being conducted on new anti-viral treatments, with both chemicals and immune response modifiers (e.g., alpha-interferon). Monoclonal antibodies are being used for new diagnostic tests for hepatitis B, cancer, AIDS, and thyroid conditions. Therapeutic applications are also under investigation. All of these projects profit from Wellcome's technology in mass tissue culture of mammalian cells. Recombinant DNA technology is being used to produce novel vaccines against hepatitis B, malaria, and foot-and-mouth disease. There are collaborations with university centers as well as contracts with U.S. biotechnology companies such as Genex and Genetics Institute. The Wellcome Foundation has joined the Terry Fox Medical Research Foundation in establishing the Biomedical Research Center on the campus of the University of

British Columbia in Vancouver, Canada, for research on the therapeutic application of biological substances.

Start-Ups Under Government Sponsorship

The U.K. government has been an active participant in the creation of five new biotechnology companies. These companies capitalized on the research done at the nuclear research center in Harwell (Amersham), the MRC (Celltech and its spin-offs), and the AFRC (Agricultural Genetics Company). Though initially funded by the government (totally or in part), the government stake will eventually be sold. In addition, the Scottish Development Agency has provided most of the funding for the construction of Scottish production facilities for Damon Biotech, a U.S. company.

AMERSHAM started as part of the Harwell nuclear center, was established as a state-owned company in 1971, and was privatized in 1982. Its principal business has been the production of radioisotope-labeled compounds for medical and research uses. It has a staff of 3,000, the majority of whom are in the U.K. Amersham is essentially an export business, with 90 percent of its production sold abroad (Table 5) (32). It shares the world market with New England Nuclear Corporation, a DuPont subsidiary. Amersham has three product divisions: medical, industrial and research.

Amersham has a heavy commitment to research [budget approximately 10 percent of sales (33)] and its strategy is to move away from radioactive products (a mature market) and to apply new technologies such as monoclonal antibodies, enhanced luminescence, and enzyme amplification. For this purpose, they have approximately 100 collaborative agreements with universities in the U.K., the U.S., and Germany (32). In this manner, they can get custom production of groups of special monoclonal antibodies and pursue development of non-radioactive antibody detection systems. This should result in diagnostic kits and assays with broader markets than labeled ones.

Amersham has contracted with a Japanese company for production of restriction enzymes, an addition to their product line. This is a further step in their policy of providing comprehensive support to the research community. Long-term research is directed towards protein technology and development of biosensors.

CELLTECH and Its Offspring:

There was considerable consternation in the U.K. when it was realized that the process for monoclonal antibodies discovered in a MRC laboratory had never been patented. The U.K. government then decided to establish a company for the commercialization of new discoveries in the MRC laboratories. Celltech was created in 1980, with an initial capitalization of £12 million ($15.56 million), 44 percent provided by the BTG, and the remaining 56 percent by large investors such as Midland Bank and Prudential. BTG first reduced its investment to 28 percent, then to 15 percent, then to nil in 1986. In 1985, 95 percent of Celltech's sales were exported (Table 5), 45 percent to the U.S. (34).

Table 5.
Charecteristics of Government Initiated Companies

	Apcel	Boots-Celltech	Celltech	Agricultural Genetics Company	Amersham
Annual Sales 1985	£600K ($777.8k)*	£1.461M ($1.89M)	£3.8M ($4.9M)	£87,273 ($113,130)	£119.76M ($155.24M)
Net Profit or Loss		-£1.111M (-$1.440M)	-£1.415M (-$1.834M)	£552,564 ($716,288)	£12.27M ($15.9M)
Business Sectors	Contract R&D Streptavidin Streptomyces Antibiotics	Immunodiagnostic assays Contract R&D Hormonal assays	Blood group reagents Human gorwth hormone Calcitonin Tissue plasminogen activator Tumor necrosis factor Macrophage activating factor	Improved plants Microbial inoculants & biological control agents Tissue culture & micropropagation Contract R&D	Immunodiagnostics Nulear medicine Radiation sources for incorporation into instruments or measurement systems Convenience products for rDNA work Restriction enzymes
Areas of R&D	Microbial genetics Development of strains Fermentation Downstream processing New Antibiotics	Immunodiagnostic assays Immunoflourescent tests Veterinary & human fertility predictor assays	Mammalian cell culture Calcitonin Tissue plasminogen activator Tumor necrosis factor Tissue inhibitor of metallo proteinases Human growth hormone	Improved plants Tissue culture Genetic manipulation	Genetic engineering of monoclonal antibiodies NRIA Radioactive materials Health physics monitoring equipment Robot arms for assembly of radiation sources w/in shielded enclosures
Academic Relationships				Cambridge University	University of Missouri

*Average exchange rate for 1985: £1=$1.2963, k=thousands, M=millions
SOURCE:1985 Annual Report of Accounts from each respective company.

Celltech has two principal assets: its initial ties to the MRC and its capabilities in the production of biological products by large-scale tissue culture of mammalian cells. Its major products appear in Table 5. The original agreement with MRC gave Celltech the rights-of-first refusal on any MRC discoveries. This was cancelled in 1983, because the government felt that the process was slow and inefficient. Celltech has an agreement with the BTG to fund MRC projects with the BTG receiving 0.5 percent of total sales plus royalties (35). Research support comes from: (1) DTI, (2) collaborative grants from MRC and SERC, (3) BTG, (4) EEC, and (5) regional authorities. Of these, the DTI innovation grants are the most important.

Though it is no longer the sole industrial conduit for the MRC, Celltech maintains close ties to MRC laboratories and scientists, and uses them not only for keeping abreast of the science, but also for recruitment. Celltech shares many of the characteristics of the more successful new, U.S. biotechnology companies. At the same time, it is the standard bearer for the new, U.K. biotechnology companies. Celltech announced its first major agreement in April 1986. Under a $7.5 million, 2-year contract with American Cyanamid, Celltech will develop improved monoclonal antibodies for "in vivo" imaging and treatment of various forms of cancer. In addition to the initial investment, American Cyanamid will eventually pay royalties and licensing fees to manufacture the products developed (36). While Celltech has maintained its focus on products for human health care, it has taken the unusual step of spinning off three new businesses: Boots-Celltech (diagnostics), Apcel (industrial microbiology), and Biocommerce Data (information services).

Boots-Celltech is a joint venture between Boots (the U.K.'s largest retail drugstore chain) and Celltech for the development of diagnostic kits. Celltech's expertise in the production of monoclonal antibodies is a major resource while Boots provides an extensive retail network. The company already has a staff of 100, and has developed an assay for TSH and is currently in the process of producing assays for infectious diseases, chlamydia, herpes, alpha- and gamma-interferon, follicle stimulating hormone, and LSH. Boots-Celltech has projected sales of £5 million ($6.48 million) for 1986 (37). In addition to human health care products, there is also R&D directed towards fertility products for cows. A subsidiary has been established in New Jersey in order to market their products in the U.S.

Apcel is a joint venture between Celltech and Air Products, a U.S. company, who had decided to diversify into new business areas such as ceramics and biotechnology. Apcel has a staff of 39, 25 of whom are in R&D. Its principal business is the development of bacteria and yeast strains for industrial fermentation and downstream processing. Apcel has contracts with Air Products and Celltech, and also with outside firms (50 percent of turnover). Sales have increased from £600,000 ($777,800) in 1985 to an expected £1.2 million ($1.55 million) for 1986 (38). Apcel also carries out its own R&D in order to create its own products and processes focusing on streptomyces and the modification of antibiotic pathways, particularly cephalins. They are also studying the use of bioconversion for the production of fine chemicals. One of the dilemmas facing Apcel is that in addition to providing R&D services to its parent companies, it would also like to establish its own corporate identity with its own product line.

Celltech also had developed an information service that abstracted technical and commercial information on biotechnology. This service was used for Celltech's business strategy, and also provided assistance to other biotechnology companies. Early in 1986, Biocommerce Data was spun off as a separate, privately owned company. It publishes "Abstracts in Biocommerce," and provides biotechnology data services to private companies. Sales for 1986 are expected to be £150,000 ($194,500), about equally divided between sales of the abstracts and information services (39).

The Agricultural Genetics Company (AGC) is the most recent creation of government policy in pursuit of commercialization of government funded basic research. Its primary objective is to exploit the basic research carried out in the laboratories of the AFRC.

AGC's approach was intrinsically different from that of Celltech, and Amersham before them, in that it did not intend to operate its own laboratories. The initial investors were the BTG (22 percent), Advent (10 percent), Ultramar (26 percent), and AFRC. AGC raised £17 million ($22.04 million) in 1983, and acquired rights-of-first refusal on AFRC research in areas relating to non-traditional plant breeding (40). It has a staff of 29, and works with AFRC scientists to identify possible products or processes. AGC can then choose to exploit the discovery itself or enter into a joint venture with other companies. Since AGC lacks its own laboratories, the R&D work is contracted out to university or AFRC laboratories. AGC operates its New Plant Product Laboratories (NPPL) subsidiary at the Rothamsted Experimental Station, which produces seeds treated with Rhizobium to reduce fertilizer requirements. Though AGC is believed to have great potential, there has been dissatisfaction with the relationship voiced by both the company and the AFRC scientists. The former has felt that the scientists have unrealistic views of the commercial value of their research, while the latter have expressed the view that they would be better off commercializing their own research.

The New Biotechnology Companies

In addition to the state-assisted, new companies, the U.K. has a relatively large number of new, small companies, similar in many ways to their U.S. counterparts. Table 6 provides a summary of the new companies visited: three in the Cambridge area, one in Wales and one in Scotland.

Of the five, PA Technology is the only large one, but its main business is management consultancy. A new business area is development of products, processes and business strategies in technology areas of which biotechnology is one. They do this under contract for other companies. In biotechnology, PA Technology has a turnover of £12 million ($15.55 million) per year in the U.K. and abroad (41). Their primary project areas appear in Table 6, with much of their business outside the U.K. While they receive 85 percent of their contracts from private industry (41), part of the research is contracted to universities or other organizations. PA's strength is that it is able to offer an integrated package of R&D, commercial assessment and management consultancy. Up to now, it has not spun off any new companies, but this has begun to change as it identifies new business areas.

Table 6.
New Biotechnology Companies Visited

	Bioscot	Biotechnica	Cambridge Life	IQ(Bio)	PA Technology
Annual Sales 1985	£200k ($259.3k)*	£223k ($289.1k)	£180k ($233.33k)	£750k ($972.2k)	£140M ($181.5M)
Profits 1985	none	-£294k (-$381.1k)	none	none	---
Capital Investment	£1M ($1.2963M)	£1.8M ($2.33M)	£2M + £1.5M ($2.59M + $1.95M)	£3.5M ($4.53M)	
Products	Agent for contract R&D Monoclonal diagnostic kits for fish diseases Blood typing Diagnostic kits for potato & fruit viruses	Microbial inoculant for silage making Mycorrhizal fungi to promote plant growth Use of fungal inoculants to improve seedling survival Herbicide degradation Biological decontamination of land	Assay for tylenol Test for methotrexate Assay for albumin Development of biosensors using antibodies, enzymes or whole cells	Assay for thyroid stimulating hormone Veterinary kit for progesterone Kits for chlamydia, hepatitis, herpes Applications for enzyme amplification techniques	Management consultancy Personal services Computers & telecommunications P.A. Technology-contract R&D in: -plant biotechnology (flavors, fragrances) -biosensors -biological production of bulk chemicals
Academic Relationships	Edinburgh University Heriot-Watt University	University of Wales		Cambridge University	Cambridge University University of Bath

*Average exchange rate for 1985: £1=$1.2963. k=thousands, M=millions
SOURCE: 1985 Annual Report of Accounts from each respective company.

Three of the companies [Bioscot, Cambridge Life Sciences, and [QBio)] have concentrated on the diagnostics market. However, their approaches differ. Bioscot is a joint enterprise between Edinburgh University and Heriot-Watt University with the research being carried out at the university laboratories. The projects selected involve certain missions mandated to government agencies in public health and agro-food (e.g., diagnostics for fish diseases to the Fisheries Department, blood typing by the Scottish National Blood Transfusion Agency). Cambridge Life Sciences identified market niches that had limited competition (e.g., assay for Tylenol overdoses) and are planning for the long-term development of biosensors. IQ(Bio) has made use of enzyme amplification as a substitute for radioisotope-based assays. They have developed a number of diagnostic kits for TSH and certain infectious diseases, as well as a progesterone kit for cows. IQ(Bio)'s enzyme-coupled reactions are being developed further with a two-step process and this is also being applied to DNA. Biotechnica uses microbial inoculants for environmental and agricultural problems and is an affiliate of the U.S. company Biotechnica International. The use of microorganisms for treatment of landfills in situ with possible production of methane gas for commercial use is of particular interest. The same technology can also be applied to contaminated land which could not be otherwise used for development.

BIOTECHNOLOGY INVESTMENTS LIMITED (BIL):

Venture capital and investment in new biotechnology companies are fairly new activities in Western Europe. The total equity in venture capital in Western Europe is ECU 5.7 billion ($9.26307 billion)* with the U.K having the largest share (43 percent) followed by the Netherlands (18 percent) (42). In biotechnology, one of the most important funds is Biotechnology Investments Ltd., advised by N.M. Rothschild. BIL was established in 1981 with an initial capitalization of $46 million, followed by a second round of $25 million in 1984 (43). BIL has expanded its investments from biotechnology into medical devices and equipment. Approximately 75 percent of their investments are in the U.S. and 25 percent in the U.K. (43). The establishment and development of new high technology companies requires a thorough understanding of the political and commercial environment of a specific country and a network of important contacts among its scientists and managers. For BIL, only the U.S. and U.K. meet these requirements at present.

INDUSTRIAL OVERVIEW

The industrial sector provides an embarrassment of choices, though not necessarily of riches. The U.K. has a broader spectrum of companies and industrial activities than any other country in Europe. In addition, many of the larger U.K. companies have been successful in establishing themselves in the U.S. market. The four large multinationals described in this study, have done well, particularly in the pharmaceutical sector. Glaxo and ICI rank 18th and 20th worldwide, respectively, among the most important pharmaceutical companies. Except for ICI, their attitude towards biotechnology remains

*Average exchange rate for 1985: European currency unit (ECU) 1 = $1.6251.

guarded, and a high proportion of their R&D is along well established lines. They have shown a conservative attitude towards external research (either in cooperation with university laboratories or contracted to smaller companies). They are confident that only large companies will be able to exploit the new biological techniques. ICI has been unusual among the multinationals in its commitment to biotechnology and the development of new biological business areas, although some of these have not been commercially successful (e.g., single cell protein). ICI has not only diversified its pharmaceutical R&D, but it has also made major efforts in plant biotechnology, biopolymers and industrial enzymes.

The U.K. has been sensitive to the long standing criticism that it has not fully exploited its own research achievements (or those of others). This has resulted in the interesting phenomenon of the government being directly involved in the creation of a number of new companies. Involved in this exercise are the MRC, AFRC, DTI, and BTG. Three separate mechanisms have been tried: (1) spin-off from a major research establishment (Amersham), (2) creation of a company to exploit MRC research (Celltech), and (3) creation of a company that acts as a contractor/agent for R&D carried out in AFRC laboratories (AGC).

Amersham was created by splitting off part of the Harwell Nuclear Facility involved in the production of isotope-labeled compounds. It is now a well established, profitable operation that has benefitted from the growth of the research market and of biomedical applications. It has invested heavily in R&D and maintained close ties with the research community in the U.K. and abroad.

Celltech and AGC have emerged from a different concept. They were intended to commercialize the basic research of the MRC and AFRC, respectively. Both have had difficulties in finding an effective mechanism of technology transfer and in focusing their activities. Celltech has concentrated on the technology of large-scale mammalian cell culture for the production of monoclonal antibodies and new therapeutic agents (e.g., human growth hormone). AGC differs from Celltech in that it does not operate its own laboratories. Instead, AGC develops its products through contracts to AFRC laboratories, either alone or in cooperation with another company. The same difficulties encountered by Celltech may eventually lead AGC to become a more conventionally structured company with its own staff and product line.

Apcel and Boots-Celltech are similar to the start-up companies shown in Table 4. PA Technology differs, in that it is part of a management consultancy group and is primarily involved in R&D rather than production. These small, new companies are characterized by a low level of capitalization [£1-5 million ($1.29-$6.48 million)] and a product line directed towards a small and well defined niche. This inevitably leads to difficulty in generating the sales necessary for expansion unless they find larger partners and/or successfully move into the U.S. market. Biotechnica is associated with a U.S. firm, while at least two of the others are in the process of establishing themselves in the U.S. The obvious alternative is to enter into agreements with companies in the EEC, but this is considered to be more difficult. The relationship of most of these small firms with universities is good, but they still have found it difficult to attract senior scientists and experienced managers.

One issue in which there is broad agreement among all companies, large and small, is the negative impact of the government's policies on science and education. It is felt that the severe budgetary cuts are reducing the quality and the quantity of U.K. research and creating a "brain drain." ICI was more vocal than most, but its view that an increased proportion of its R&D may be done abroad is shared by several of the other large companies. Difficulties with staffing and access to a larger research establishment have been among the reasons mentioned.

VI. CONCLUSION

The U.K. stands at a crucial turning point in its development of high technology industries, and most specifically, in the area of biotechnology. In comparison to its European partners, it has certain major advantages: a still impressive research establishment, a large number of entrepreneurial, new biotechnology companies, and the largest pool of venture capital outside of the U.S. The great irony is that the success or failure of biotechnology in the U.K. may depend, in great part, on the policies of the Thatcher government, a strong proponent of market forces and private enterprise.

Though the U.K. government had realized the significance of the new advances in biological research, it had decided not to create a National Program in Biotechnology, as did most of the other European countries. Instead, it has made biotechnology one of the priority areas in the different government agencies, such as the research councils and the DTI. Basic research in the U.K. has been conducted primarily in the laboratories of the universities and the MRC and AFRC. This research has been impressive, both in its quality and breadth, covering subjects as diverse as genetics, neurobiology and biochemical engineering. During the long period of retreat from empire and economic decline, basic research and education had remained relatively protected, and this was a sector in which the U.K. could pride itself in remaining a first-class power. The decision of the Thatcher government to apply the same budgetary cuts to science and education that it has imposed in other government sectors has changed this. It is generally accepted that the resources have diminished, leading to consolidation of institutes, closing of laboratories, laying-off of scientific staff, and inability to pursue new research projects.

Possibly one of the most serious effects is the gradual demoralization of the research community. As one research director said, "You must have noticed that everyone is just damned tired, and dreadfully depressed. You spend all your time at meetings, writing proposals and memos -- all to no avail. And you just don't have time to do research." Or perhaps more sadly, one professor said, "I advise my best students to go abroad, there are just no career opportunities here."

According to the government, the reduced budgets should eliminate waste and establish scientific and industrial priorities as well as encourage researchers to be more entrepreneurial (both by obtaining industrial support and creating new companies). During the course of this study, there has been no evidence that there is any coordinated policy beyond the strict budgetary limits. This can be illustrated by the following:

(1) The assumption is that the U.K. will continue to do R&D and technology transfer in all biological areas, though it cannot afford to do so with the existing budgets.

(2) The U.K. has experimented with more mechanisms of technology transfer than any other country, but there is no agreement on its goals or on mechanisms for its evaluation.

(3) The government has had an important role in establishing certain new biotechnology companies. However, it is not clear whether its support of certain standard-bearers is more effective than financial assistance of privately initiated new companies. There is even the curious situation of the Scottish Development Agency providing £30 million ($38.9 million) to Damon Biotech, a U.S. company (44), to establish a production facility in Scotland. This company is an active competitor of Celltech, one of the first government-supported biotechnology companies.

(4) There is potential overlap between the industrial innovation activities of the Biotechnology Directorate of SERC and the Biotechnology Unit of DTI.

(5) Government policy is intended to increase industrial support of basic research in the U.K. Instead, the weakening of the science base has made major U.K. multinationals, such as ICI and Glaxo, expand their R&D activities in the U.S. NHS policies have led to a reduction in U.K. R&D by foreign multinationals.

The excellence of U.K. research today has seldom coincided with an equal success in its commercialization. The blame has been laid, with some justification, on the shoulders of the scientists. However, British industry has not been particularly innovative in its R&D or in its interactions with the research community. Many researchers and new biotechnology company officials found a more positive response from U.S. and other European companies than from U.K. companies. This is due in part to the small number of important large companies and to their policy to carry out their research in-house. Another important factor identified by a number of analysts is that many of the senior managers have a financial background, and are consequently not very comfortable with new technologies and their corresponding new products and markets.

The dilemma is that the U.K. today represents a significant proportion of the basic research and new industrial activity in the European community. Given the economic situation in the U.K., it is unlikely that any government can avoid a reduction in basic research. In the industrial sector, the long-term prospects for new sectors, such as waste treatment, biosensors, marine biology, and enzyme technology are excellent, but most new U.K. companies are undercapitalized, and lack the resources for expansion. The U.K. could ally itself more closely to the EEC, both through government programs that might assist its basic research, and through agreements with European companies in the development of new products and processes. Political and commercial factors will make this a slow process at best.

The other alternative is in closer ties to the U.S., something that we have already observed in some of the larger companies. Certainly at the industrial level, it can be expected that there will be an increase in the number of agreements between U.S. and U.K. companies (including many of the smaller ones). Though here, as in other issues, this will be sharply affected by government policy which is extremely sensitive to anti-American feeling from a substantial part of the population. This surfaced recently during the debate on the sale of the Westland helicopter company, and of divisions of British Leyland, to American companies.

In conclusion, the U.K. has important scientific and industrial resources which are unlikely to be exploited without major foreign partners. How the U.K. will emerge from this crucial period will be strongly dependent on government policy in this respect.

ACKNOWLEDGMENTS

Gloria Coats, Industry Specialist, Foreign Commercial Service, American Embassy, London

Michael Mercurio, Commercial Attache, Foreign Commercial Service, American Embassy, London

Becky Roberts, Research Assistant, Biotechnology Program, Foreign Commercial Service, American Embassy, London

REFERENCES

1. Semi-Annual Economic Trends Report, American Embassy London, November 1985.

2. Medical Research Council Annual Report for 1984/85.

3. Alwen, John, Secretary of the Cell Board, Medical Research Council, London, personal communication, January 1986.

4. Crisis in Research, Office of Health Economics, London, 1986

5. Agriculture and Food Research Council Annual Report, 1984-85.

6. Jamieson, Brian, Assistant Secretary for Plants, Soils & Engineering Research, Agriculture and Food Research Council, personal communication, January 1986.

7. Financial Times, London, June 16, 1986.

8. Science & Engineering Research Council Corporate Plan, December 1985.

9. Moffat, Anne Simon, "British Research Council & Industry Sign Protein Engineering Agreement," Genetic Engineering News, March 1986.

10. Financial Times, London, July 28, 1986.

11. Financial Times, London, January 16, 1986.

12. Laboratory of the Government Chemist, the Biotechnology Unit, September 1985.

13. Dietz, Roy, Head, Biotechnology Unit, Department of Trade & Industry, London, personal communication, December 1985.

14. A Collaborative Research Initiative in Biotechnology, Laboratory of the Government Chemist, Department of Trade & Industry, September 1985.

15. Bailey, Peter, Science Technology Transfer Division, British Technology Group, London, personal communication, May 1986.

16. British Technology Group Review, 1985.

17. Financial Times, London, January 6, 1986.

18. Financial Times, London, January 17, 1986.

19. Financial Times, London, June 20, 1986.

20. Financial Times, London, January 17, 1986.

21. Annual Report & Accounts, Glaxo Holdings p.l.c., 1985.

22. Williamson, A.R., Research Director, Glaxo, personal communication, January 1986.

23. Rodgers, Peter J., Biochemical Group Manager, Imperial Chemicals Industries, Runcorn, personal communication, March 1985.

24. Windass, John, Molecular Biology Program, Imperial Chemical Industries, Runcorn, personal communication, January 1986.

25. Financial Times, London, February 28, 1986.

26. Bridges, Ian, Plant Biotechnology Group, Imperial Chemical Industries, Runcorn, personal communication, January 1986.

27. Financial Times, London, August 1, 1986.

28. Financial Times, London, April 7, 1986.

29. Financial Times, London, January 31, 1986.

30. Wellcome Annual Report, 1985.

31. Castell, W.M., Managing Director, Wellcome Biotechnology Inc., personal communication, January 1986.

32. Maynard, J.C., Chief Executive, Research Products Division, Amersham International, March 1985.

33. Financial Times, London, June 17, 1986.

34. Thomas, David, Business Director, Celltech, Slough, personal communication, April 1986.

35. Foden, Sue, Academic Relations, Celltech, Slough, personal communication, April 1986.

36. Chemical Week, May 14, 1986.

37. Baker, Terry, Director of R&D, Boots-Celltech, personal communication, May 1986.

38. Humphreys, Gwyn, Director of R&D, Apcel Ltd., personal communication, May 1986.

39. Crafts-Lighty, Anita, Managing Director, BioCommerce Data, personal communication.

40. Gilmour, Roger, Managing Director, Agricultural Genetics Company, Ltd., personal communication, August 1986.

41. Tonge, Glyn, Divisional Director, PA Technology, personal communication, April 1986.

42. Financial Times, London, July 19, 1986.

43. Leathers, David, Director, Biotechnology Investments Limited, personal communication, March 1985.

44. Financial Times, London, July 26, 1985.

APPENDIX

Institutions and Individuals Visited

Government

AFRC: Mr. Brian Jamieson, Assistant Secretary; Mr. Nick Wingfield.

MRC: Dr. John Alwen, Secretary of the Cell Board: Mr. Bill Matthews, Industrial Liaison Officer.

SERC: Dr. Geoffrey Potter, Director, Biotechnology Directorate.

DTI: Dr. Ronald Coleman, the Government Chemist; Dr. Roy Dietz, Head, Biotechnology Unit.

BTG: Dr. Peter Bailey, Science Technology Transfer Division.

Universities and Research Institutes

Biotechnology Centre, Cambridge University: Dr. Christopher Lowe, Director.

Department of Molecular Biology, Edinburgh University: Dr. Noreen Murray, Lecturer.

Centre for Biotechnology, Imperial College of Science and Technology, London: Professor M. Lilly, Director.

Leicester Biocentre, Leicester University: Dr. John Higgins, Director; Dr. Barry Holland, former Director.

King's College, London University: Professor Peter B. Gahan, Assistant Principal.

MRC Laboratory of Molecular Biology, Cambridge: Dr. Sydney Brenner, Director.

John Innes Institute, Norwich: Dr. D.A. Hopwood, Head, Genetics Department; Dr. P.J. Shaw, Cell Biology; Dr. J.W. Davies, Head, Virology Department.

Plant Breeding Institute, Cambridge: Dr. Peter Day, Director; Dr. Richard Flavell, Head, Molecular Genetics Department.

Rothamsted Experimental Station, Harpenden: Dr. Leslie Fowden, Director; Dr. Peter Shewry, Head, Department of Cell and Molecular Biology.

Companies

Agricultural Genetics Company, Cambridge: Dr. Roger Gilmour, Managing Director.

Amersham International, Amersham: Dr. J.C. Maynard, Chief Executive, Research Products; Mr. E.A. Evans, Business Manager.

Apcel, Slough: Dr. Gywn Humphreys, Director of R&D.
Bioscot, Edinburgh: Dr. Bruce Haddock, Managing Director; Mr. Terry Dobson, Business Manager.

Biotechnica Ltd., Cardiff: Dr. Stirling Hogarth-Scott, Managing Director.

Boots-Celltech, Slough: Dr. Terry Baker, Director of R&D; Dr. John G. Simpson, Assistant Director.

Celltech, Slough: Mr. David Thomas, Manager, Human Resources and External Relations; Dr. Sue Foden, Business Manager.

Glaxo, Greenford: Dr. A.R. Williamson, Research Director.

Imperial Chemical Industries

- -Agricultural Division, Billingham: Dr. Peter Rodgers, Biochemical Group Manager.

- -Marlborough Biopolymers, Stockton-on-Tees: Dr. John Adsetts, Chief Executive.

- -Corporate Bioscience Group, Runcorn: Dr. Michael Rose, Group Manager; Dr. John Windass, Dr. Ian G. Bridges, Research Associates; Mr. David Oxlade, Director Marketing and Business Development, Diagnostics Group.

IQ(Bio), Cambridge: Dr. Roger B. Cox, Commercial Director; Dr. Axel Johannsson, Research Director.

PA Technology, Royston: Professor G.M. Tonge, Division Director.

Wellcome Biotechnology, Beckenham: Dr. W.M. Castell, Managing Director; Dr. John Beale, Scientific Director.

Others

BioCommerce Data Ltd., Slough: Dr. Anita Crafts-Lighty, Managing Director.

Biotechnology Investments Ltd., London: Mr. David Leathers, Director.

Coopers & Lybrand, London: Mr. Edward Kostin, Director of International Tax and Planning.

Financial Times, London: Mr. David Fishlock, Science Editor.

SECTION J

INTERNATIONAL PROGRAMS IN BIOTECHNOLOGY IN WESTERN EUROPE

SUMMARY

There are three European programs that directly affect biotechnology. They have been established by the European Molecular Biology Organization (EMBO), the European Economic Community (EEC), and EUREKA. The EMBO is a scientific organization concerned with basic research, scientific exchange, and training. It also operates the European Molecular Biology Laboratory (EMBL), a major international research laboratory. The biotechnology programs of the EEC have the goal of creating a favorable environment for the development of biotechnology. This has been done by providing contracts for basic research in priority areas and for training. EUREKA is a highly political concept that seeks to promote collaboration between different European companies and organizations, not only at the precompetitive R&D stage, but also in bringing new products and processes to market. EUREKA is still at an early stage, with major differences of opinion over the role of government and the degree of public funding.

I. INTRODUCTION

There has been increasing concern in Europe about the loss of industrial competitiveness in the high technology sector. Europe, as a whole, spends as much on research and development (R&D) as does the U.S., and more than Japan. In many areas, the quality of research is equal to, or even superior to, that carried out in laboratories elsewhere. It is in technology transfer and industrial innovation that Europe seems to lag behind its main competitors.

Many of the principal European nations have established major programs in biotechnology to promote both research and industrial applications. As the pace of research has accelerated, individual countries have found it increasingly difficult to find the necessary resources to solve complex R&D problems. This has led to the creation of three European programs directed towards increasing collaboration across national borders. The oldest program is the European Molecular Biology Organization (EMBO), which has focused on basic research and training. The biotechnology programs of the European Economic Community (EEC) have focused on basic research and training. In addition, they have been concerned with building up the scientific infrastructure. The purpose of the more recent EUREKA program is the establishment of cooperative industrial projects between companies and organizations in different countries.

II. EUROPEAN MOLECULAR BIOLOGY ORGANIZATION (EMBO)

The EMBO was first envisioned as the biological counterpart of the European Center for Nuclear Research (CERN) and the proposal drawn up in 1963 included the following missions (1):

(1) creation of a European Molecular Biology Laboratory,

(2) establishment of a clearing-house for biological information,

(3) creation of a network of European laboratories, and

(4) creation of a European Fund that would provide grants to research laboratories.

The first objective to be met was the creation of the fellowship program with funds provided by the Volkswagen Foundation [DM 1.748 million ($687,000)]. The active support of the Swiss government brought together a number of European governments to create the European Molecular Biology Conference (EMBC), which is an intergovernmental organization. The member nations contribute to the EMBO budget, and at the present time, membership consists of the EEC countries, the Scandinavian countries, and Israel. The EMBO is a private organization with a membership of individual scientists who establish the scientific direction of its activities and are responsible for its budget. This two-tier system effectively serves to isolate the scientific process from political pressures.

The EMBO program costs approximately DM 10 million ($3.4 million)* per year, most of which is spent on fellowships, courses, and workshops (2). In 1985, there were 304 applications for short-term fellowships, of which 221 were awarded; 428 applications for long-term fellowships, of which 166 were awarded; 16 workshops; 21 courses; and the EMBO Symposium (3).

In 1974, the European Molecular Biology Laboratory (EMBL) was created in Heidelberg, West Germany. The EMBL is administratively separate from the EMBO, and the member nations each make a contribution to its operational budget, which is now DM 50 million ($16.98 million) per year (4). In its original conception, the EMBL was supposed to be a unique research center, conducting work that could not be done elsewhere in Europe. The focus was on the development and use of new equipment and methods for the structural analysis of biological macromolecules. The results were mixed during the initial stage, and under a new director, the scientific policy of the laboratory has undergone a major change.

The EMBL has seven Programs (research groups), which concentrate primarily on biological topics, particularly in the areas of cell and developmental biology, and the potential implications of such studies to cancer. The Cell Biology Program studies cellular organization and function in an attempt to obtain a more comprehensive view of how organisms function.

The Differentiation Program consists of nine working groups in related areas, including the mechanisms of action of growth factors, receptor-like onc genes and nuclear onc genes. The recently launched Gene Structure and Regulation Program has the primary goal of contributing to progress in DNA replication and protein engineering using bacterial plasmids and at the same time developing new tools and techniques for rDNA technology.

*Average exchange rate for 1985: Deutsche mark (DM) 2.9440 = $1.

The Biochemical Instrumentation Program is involved in extensive collaboration with other Programs within the EMBL, in the use of a modular system allowing oligonucleotide synthesis, high sensitivity protein sequencing and peptide synthesis. This Program is also trying to develop a system for automatic DNA sequencing using radioactive and flourescent probes. The Biological Structures Program includes study in x-ray crystallography, membrane proteins, and electron microscopy.

The Physical Instrumentation Program has focused its efforts on microcomputing and interface, as well as laser spectroscopy and laser microscopy. The Biocomputing Program exists to apply computing techniques to problems in experimental and theoretical molecular biology.

The organization of the EMBL is unusual for Europe, in that there are no permanent staff members (4). This provides an opportunity for setting up new research topics, staffing groups with young scientists, and carrying out the most innovative research. It also provides young scientists, from countries with limited resources, with the possibility of setting up their own groups at a major center. The EMBL's mandate applies only to basic research. It is not involved in technology transfer. Nevertheless, a number of measures have been taken to provide some assistance to European industry. These are:

(1) operation of a data bank on DNA sequences,

(2) proposal for a biocomputer program to apply computer technologies to studies on the structure of biological molecules,

(3) participation of staff members as consultants to industry and licensing of novel equipment designs and processes, and

(4) establishment of a European Ph.D. program at the EMBL.

From the beginning, the EMBL has been more controversial than its parent organization. Critics point out that if the EMBL is just one more European laboratory, then the funds used for its operation could just as easily be spent in national laboratories. This debate has sharpened as European governments have had to face increasingly severe budgetary constraints.

The rapid expansion of biological research has also led to a major increase in the number of scientific papers published. European scientists have been concerned about the major role of U.S. publications and the potential impact on European science. The EMBO established the "EMBO Journal" as a counterbalance to the large number of U.S. publications. Aided by high scientific standards and rapid publication of manuscripts, the EMBO Journal has proven quite successful (2).

III. THE BIOTECHNOLOGY PROGRAMS OF THE EUROPEAN ECONOMIC COMMUNITY

The Forecasting and Assessment in Science and Technology Program (FAST) was established for the period 1978-83, and in collaboration with other services of the Commission, developed a strategy for biotechnology in Europe.

The initial concept was that FAST would go beyond R&D to include Community-wide issues, such as training and the cost of feedstocks.

The Biomolecular Engineering Program (BEP) was the first to be established, for the period April 1982 to March 1986, with a budget of ECU 15 million ($9.23 million)*. The primary objective was the application of modern biochemistry and molecular genetics to agriculture and to agro-food industries. The principal mechanisms were research contracts, on a shared-cost basis, and training contracts for postdoctoral fellows. In the case of research contracts, the EEC paid 20-50 percent of the costs, with the remainder coming from national sources (5).

There is also the European Cooperation in the Field of Scientific and Technological Research (COST), which encourages collaboration between EEC and non-EEC European countries, such as Sweden and Switzerland. This program allows for EEC funding of one-twelfth of the cost of the project (6). During the period 1982-83, 293 applications for research funding were received, leading to the award of 106 research contracts with a duration of 24-40 months. The criteria for selection were scientific competence and relevance to the program priorities. These priorities were:

- development of second generation bioreactors,
- animal husbandry and agro-food applications,
- upgrading of plant products,
- genetic engineering of plant cells and soil microorganisms, and
- risk assessment and methods for detecting contamination in industrial processes.

There were 200 applications submitted for training programs and 84 contracts ranging from 6 to 24 months were awarded, most of them involving principal European research centers. In addition, 16 multidisciplinary meetings were held involving participants in the program, and these were instrumental in setting up networks of European laboratories working on similar projects.

The assessment of BEP concluded that the research had been satisfactory in establishing methodology for new vaccines, development of bioreactors involving co-immobilization of microorganisms and enzymes, use of multi-enzyme systems, transfer of genes into monocotyledons, and isolation and characterization of 20 different plant genes (in 16 different laboratories) (5).

The weaknesses of the program were the low level of funding (average of ECU 50,000 ($30,767) per lab per year), which essentially provided for the

*Average exchange rate for 1985: European currency unit (ECU) = $1.6251.

salary and research expenses of one scientist; the small budget, which limited the number of priority areas in the Program; and the level of industrial involvement, which was disappointingly low.

The Concertation Unit for Biotechnology in Europe (CUBE): In 1983, the Commission defined six priorities in biotechnology. These are:

(1) research and training,
(2) demonstration projects,
(3) new policies for agricultural products used industrially,
(4) agreement on European regulations,
(5) agreement on European intellectual property rights, and
(6) concertation of biotechnology policies.

In 1984, the Commission created the Biotechnology Steering Committee, which is responsible for the management and concertation of policies affecting, or affected by, biotechnology. CUBE acts as the secretariat for this Steering Committee, and has an annual budget of approximately ECU 1 million ($615,347). In practice, CUBE acquires and analyzes information on biotechnology, and sensitizes the various national governments to the opportunities for biotechnology. CUBE has no funds to be given out and no statutory authority. The unit can only provide information and try to persuade national governments to adopt policies that are compatible with those of the EEC and the other member countries (7).

The positive results of the BEP has led the Council to adopt the Biotechnology Research Action Program (BAP) for the period 1985-89. With a budget of ECU 55 million ($33,844,071) (8), BAP provides a continuation of BEP's activities in agriculture and agro-food technology. The larger budget also allows for development of the European infrastructure, with particular emphasis on data banks, computer modeling, collections of biotic materials, and methods for their preservation (9). There is also more research directed towards enzyme engineering, the physiology of industrially relevant microorganisms, and the tissue culture of plant and animal cells.

High priority is given to transnational projects and to those projects associated with industry. More than 1,300 laboratories have submitted proposals, and it is estimated that approximately 180 research and 250 training contracts will be awarded during the 1985-89 period. Though BAP has expanded the commitment of the EEC to biotechnology, areas such as bio-informatics, protein design, and plant biochemistry still require building up.

IV. EUREKA

Of the three programs described here, EUREKA has the highest profile, as it has attracted political participation at the ministerial level. EUREKA was unveiled by France in April 1985, as a European response to President Reagan's Space Defense Initiative (SDI), which was perceived as an effort to increase the U.S. technological lead over Europe. The key to the economic future was dependent on information and production technologies and the life sciences.

The critical fields were judged to be: computers, telecommunications, robotics, advanced materials, and biotechnology. In biotechnology, several projects were identified: synthetic seeds (with the possible introduction of new properties as well as enzymatic activities that would be useful for later processing), bioprocessing, and biosensors for use in drug delivery systems as well as in bioreactors (10). In contrast to previous programs, it was hoped that EUREKA would promote university-industry and industry-industry collaboration.

EUREKA was first discussed at a meeting of technology ministers in July 1985 (11). The first major issue was, and still is, the degree of government participation and funding. France and West Germany have argued for significant government funding, while the U.K. prefers a more market-oriented approach with funds provided by private industry. The present participants in EUREKA are the EEC countries as well as Switzerland, Austria, Norway, Sweden, Finland, and Turkey. EUREKA's charter defines eligible projects as those that (12):

- o bring together participants from more than one country,
- o offer identifiable benefits,
- o use advanced technologies,
- o aim to secure a significant technological advance,
- o have appropriate qualified partners, and
- o offer adequate financial commitment from participating companies,

Ten projects were initially accepted in November 1985, one of which was in biotechnology. This was diagnostic kits for sexually transmitted diseases and involved PA Technology of the U.K. and Biokit of Spain, at an estimated cost of £1.5 million ($1.94 million)* (13). A second series of 16 projects was accepted in January 1986, at a total estimated cost of £398 million ($515.9 million). None of these was in biotechnology (14). A third series of projects was approved in June 1986, and a fourth set of 37 projects worth ECU 730 million ($449.2 million) was announced in December of that same year. This brought the total number of approved projects to 109, of which 20 are in the area of biotechnology. There are an additional 44 projects still in the pipeline (15).

There is still a great deal of uncertainty regarding the nature of EUREKA projects, the degree of government support, and the organization of its administrative structure. Emphasis has moved away from the original military concept, toward civilian technologies and industrial cooperation. EUREKA is no longer perceived as an alternative to SDI. West Germany has announced support for 19 projects, at a cost of DM 1.6 billion ($543.5 million), with

*Average exchange rate for 1985: Pound sterling (£1) = $1.2963.

German companies and organizations contributing DM 625 million ($212 million) and the government providing DM 485 million ($164.7 million) over a period of 10 years (16). The U.K. has not committed any funds specifically to EUREKA, but U.K. companies can apply to the Department of Trade and Industry (DTI) for up to half of the research costs and 25 percent of development costs. The funds come out of the DTI R&D budget of £360 million ($466.7 million), and it is estimated that £50 million ($64.8 million) will be spent on EUREKA (17). Initially, France had made a commitment of FFr 1 billion ($116.3 million)*. This is likely to be reduced, given the present political situation. The total cost for EUREKA was estimated by France to be approximately FFr 50 billion ($5.56 billion) (18).

It is still too early to judge what form EUREKA will finally take, much less hazard a guess on its success. Certainly EUREKA has mobilized European political leaders into attempting to create a European framework for cooperative R&D and industrial innovation in high technology industries. What is less certain is whether this type of effort should be conducted at the highest political levels, with the possible use of public funds to provide an incentive for industrial collaboration.

V. CONCLUSION

A number of European countries have first-class research in their universities and government laboratories. Perhaps just as important, is the existence of major, multinational corporations with extensive R&D programs, substantial financial resources, and modern production facilities. In some countries, the industrial effort is more important than that found in the public sector. The European problem has frequently been posed in terms of inefficient technology transfer and sluggish industrial innovation. What is often ignored is that in basic research, there are serious difficulties in collaboration across national borders, mobility of scientists, and standardization of educational requirements. Though there are no detailed statistics, most of the scientists interviewed felt that European researchers were far more likely to spend time in a U.S. laboratory and/or collaborate with their U.S. counterparts than within Europe. Similar observations have been made of industrial agreements. Thus the problem can be broken down into several components:

(1) Government: Can policies affecting biotechnology within each nation be made consistent, with the ultimate goal of developing a European policy?

(2) R&D: Can scientific manpower and research funds be used in the best laboratories regardless of national boundaries?

(3) Industry: Can companies be established, collaborate, and gain access to markets, regardless of national boundaries?

*Average exchange rate for 1985: French franc (FFr) 8.9852 = $1.

(4) Networks: Can scientists, government officials, and corporate managers create European networks that allow them to collaborate at a transnational level?

Faced with these questions, European institutions have reacted in different ways. In the case of biotechnology, programs have been established by the EMBO, the EEC, and EUREKA. Though somewhat oversimplified, these three different approaches reflect different constituencies and their needs.

The EMBO is basically a scientific organization concerned with basic research, scientific exchange, and training. It operates by scientific peer review, and has managed to reconcile this process with the political realities of multinational funding. Lacking widespread support for a European grant system, its major role in basic research has been the establishment of the EMBL, which is a good European center with a multinational staff. The EMBO's courses and workshops have won extensive recognition, not only in Europe but also in the U.S. Neither the EMBO nor the EMBL have intended to, nor do they, play a major role in technology transfer.

The directorates and committees of the EEC are bureaucratic bodies that deal with the problem of "creating a favorable environment for the development of biotechnology." Since the creation of a favorable environment deals with such intractable subjects as the price of agricultural feedstocks, regulatory legislation, and tax and labor laws, the programs have been reasonably directed towards basic research, training, and scientific infrastructure, though there is also an effort at "concertation" of national policies. This represents an overlap (possibly even competition) with the activities of the EMBO, though the priorities of the EEC programs are directed towards economic and political goals. This necessarily makes the EEC programs much more political, and less dependent on strict scientific review. Given similar goals, the EEC and the EMBO could collaborate on some of their programs. The EMBL director has, in fact, proposed that some of the EEC funds should be used to support selected EMBL programs, such as those for data banks and biocomputers. To date, the EEC has not been receptive to such initiatives, partially due to the difference in the membership of the two organizations.

EUREKA is a political creation, devised initially as a response to SDI, and has been endorsed by the political leadership at the highest levels. EUREKA's goal has now been altered to that of meeting the U.S. and Japanese technological challenge. As a concept, it seeks to promote collaboration between different European companies and organizations, not only at the precompetitive R&D level, but also in bringing new products and processes to market. It is, however, still a concept in search of reality. The unresolved details center around the role of government intervention, and the degree of public funding. Though EUREKA was initially restricted to European companies, U.S. companies can now participate through their European subsidiaries. Given the rapid pace of biological research, companies with common interests in biotechnology are entering into joint ventures by themselves. Aside from an official endorsement and possible government subsidy, it is unclear how EUREKA can further stimulate this process.

The EMBO started out with relatively modest goals, the majority of which have been realized. The EEC and EUREKA programs are far more ambitious, but it is too early to judge the results. On the positive side the EMBO and the EEC have had an impact on training, and scientific exchange, and so have stimulated the creation of scientific networks within Europe. While the EMBO failed to create a research fund, the EEC funds research at a number of European laboratories, though the budget is small. Research contracts have been helpful to scientists in countries affected by budgetary problems, and have stimulated international collaboration. All of the programs, but particularly EUREKA, have sensitized policy makers and public opinion to the need for greater collaboration in the field of high technology. This is a necessary first step in the development of common policies in areas such as biotechnology.

On the other hand, the budgets involved are small, and the review process may involve political compromises that delay the final decision. The operating principle still remains that each country derives benefits in proportion to its budgetary contribution, which is not necessarily consistent with support of the best R&D or the most competitive industrial projects.

The fact remains that there is great diversity among the member nations, not only in scientific and human resources, but also in industrial profile and economic capabilities. For the weak, this argues for expansion of joint ventures and collaboration. For the strong, it is in their interest not to collaborate in those areas in which they are ahead, but only those in which they lag behind. And it is from those diverse interests and needs that common policies and decisions must be forged.

ACKNOWLEDGMENTS

Felix Dorough, Counselor, Science & Technology, U.S. Mission, European Communities, Brussels

REFERENCES

1. Tooze, John, A Brief History of the European Molecular Biology Organization, IBL Press, 1981.

2. Tooze, John, Scientific Coordinator, European Molecular Biology Laboratory, personal communication, September 18, 1986.

3. European Molecular Biology Conference, Annual Report, 1985.

4. Phillipson, Lennart, Director General, European Molecular Biology Laboratory, personal communication, September 18, 1986.

5. The Biomolecular Engineering Program (BEP) of the European Communities: Implementation activities and Preliminary Evaluation of Achievements, CGC-IV/86/2.

6. Cantley, Mark, CUBE team, personal communication, July 30, 1986.

7. Biotechnology at Community Level: Concertation, XII/85, MFC/cp/6.

8. Multiannual Research Action Programme of the European Economic Community in the Field of Biotechnology, XII/945/86-EN.

9. Communication from the Commission to the Council, Concerning the Review of the Multiannual Research Programme for the European Economic Community in the Field of Biotechnology (1985-89), COM (86) 272 Final.

10. Boniface, Pascal, and Francois Heisbourg, LA PUCE, LES HOMMES, ET LA BOMBE, L'Europe face aux nouveaux defis technologiques et militaires, Hachette, France, 1986.

11. Financial Times, London, July 19, 1985.

12. Financial Times, London, November 8, 1985.

13. Financial Times, London, November 7, 1985.

14. Financial Times, London, January 24, 1986.

15. Financial Times, London, December 18, 1986.

16. Financial Times, London, June 28, 1986.

17. Financial Times, London, March 14, 1986.

18. Financial Times, London, July 19, 1986.

APPENDIX

ORGANIZATIONS AND INDIVIDUALS VISITED

GOVERNMENT

Mark Cantley, Concertation Unit for Biotechnology in Europe, Commission of the European Communities

UNIVERSITIES AND RESEARCH INSTITUTES

Dr. Lennart Phillipson, Director, European Molecular Biology Laboratory

Dr. John Tooze, Secretary General, European Molecular Biology Organization

SECTION K

GLOSSARY

Acetic acid	A water-miscible liquid, the essential constituent of vinegar: used chiefly in the manufacture of acetate fibers and in other organic syntheses.
Aerobic	Living or acting only in the presence of oxygen.
Alimentary	Concerned with the function of nutrition; providing sustenance.
Amino acids	The building blocks of proteins. There are 20 common amino acids.
Amylase	An enzyme that is found especially in grains, meat, and vegetables and that acts on starch, glycogen and some dextrins with the formation of maltose.
Anaerobic	Living or acting in the absence of oxygen.
Analogue	An organ or part corresponding in function, but not evolved from corresponding organs, as the wings of a bee and those of a hummingbird.
Antibiotic	A specific type of chemical substance that is administered to fight infections, usually bacterial infections, in humans or animals. Many antibiotics are produced by using micro-organisms; others are produced synthetically.
Antibody	A protein (immunoglobulin) produced by humans or higher animals in response to exposure to a specific antigen and characterized by specific reactivity with its complementary antigen. (See also monoclonal antibodies.)
Antigen	A substance, usually a protein or carbohydrate which, when introduced in the body of a human or higher animal, stimulates the production of an antibody that will react specifically with it.
Applied research	Research to gain knowledge or understanding necessary for determining the means by which a recognized and specific need may be met (National Science Foundation definition).
Assay	A technique that measures a biological response.

Bacteria	Any of a large group of microscopic organisms having round, rodlike, spiral, or filamentous unicellular or noncellular bodies that are often aggregated into colonies, are enclosed by a cell wall or membrane, and lack fully differentiated nuclei. Bacteria may exist as free-living organisms in soil, water, organic matter, or as parasites in the live bodies of plants and animals.
Basic research	Research to gain fuller knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications toward processes or products in mind (National Science Foundation definition).
Biocatalyst	An agent, as an enzyme, element, etc., that acts as a biochemical catalyst.
Biochemistry	The science dealing with living matter.
Bioconversion	A chemical conversion using a biocatalyst.
Bioengineering	Engineering relating to the biosynthesis or processing of animal or plant products; specifically engineering relating to fermentation processes.
Biomass	The amount of living matter in the form of one or more kinds of organisms present in a particular habitat, usually expressed as weight of organisms per unit area of habitat or as volume or weight of organisms per unit volume of habitat.
Bioprocess	Any process that uses complete living cells or their components (e.g., enzymes, chloroplasts) to effect desired physical or chemical changes.
Biosensor	An electronic device that uses biological molecules to detect specific compounds.
Biotechnology	Commercial techniques that use living organisms, or substances from those organisms, to make or modify a product, and including techniques used for the improvement of the characteristics of economically important plants and animals and for the development of micro-organisms to act on the environment. In this report, biotechnology is used to mean "new" biotechnology, which only includes the use of novel biological techniques -- specifically, recombinant DNA techniques, cell fusion techniques, especially for the production

	of monoclonal antibodies, and new bioprocesses for commercial production.
Calcitonin	Regulates calcium level in blood. Non-biologically produced form approved in some European countries to treat osteoporosis and in U.S. to treat Paget's disease (a chronic disorder of the bones characterized by enlargement and deformity of the skull, spine, and long bones).
Cardiovascular	Relating to, or involving the heart and blood vessels.
Cell culture	The in vitro growth of cells isolated from multicellular organisms. These cells are usually of one type.
Cell differentiation	The process whereby descendants of a common parental cell achieve and maintain specialization of structure and fuction.
Cell line	Cells that acquire the ability to multiply indefinitely in vitro.
Cellulase	Any of a group of enzymes that are found in various fungi, bacteria, insects, and lower animals and that hydrolyze cellulose.
Cephalosporin	A form genus of imperfect fungi with conidia (any asexual spore not borne within an enclosing structure) held together by a slimy secretion in more or less spherical heads at the ends of the fertile branches.
Characterization	Portrayal of any trait, function, structure, or substance of an organism resulting from the effect of one or more genes as modified by the environment.
Chromatin	A complex of a polymerized nucleic acid held to be the physical carrier of genes.
Clinical trial	One of the final stages in the collection of data for drug approval where the drug is tested in humans.
Clone	A group of genetically identical cells or organisms produced sexually from a common ancestor.

Cloning	The amplification of segments of DNA, usually genes.
Co-enzymes	Any thermostable nonprotein compound that forms the active portion of an enzyme system after combination with an apo-enzyme.
Colitis	Inflammation of the colon.
Culture medium	Any nutrient system for the artificial cultivation of bacteria or other cells; usually a complex mixture of organic and inorganic materials.
Diagnostic products	Products that recognize molecules associated with disease or other biologic conditions and are used to diagnose these conditions.
DNA	Deoxyribonucleic acid. The genetic material of all living organisms. Every inherited characteristic has its origin somewhere in the code of each individual's complement of DNA.
DNA probe	A sequence of DNA that is used to detect the presence of a particular nucleotide sequence.
Downstream processing	After bioconversion, the purification and separation of the product.
Drosophila	Any of a genus of small two-winged flies used in the study of basic mechanisms of inheritance.
Drug	Any chemical compound that may be administered to humans or animals as an aid in the treatment of disease.
E.coli	Escherichia coli. A species of bacteria that inhabits the intestinal tract of most vertebrates. Some strains are pathogenic to humans and animals. Many nonpathogenic strains are used experimentally as hosts for rDNA.
Eglin	Used in the treatment of emphysema.
Electrophoresis	The movement of suspended particles through a fluid under the action of an electromotive force applied to electrodes in contact with the suspension, important applications being in the separation of colloids and the deposition on one of the electrodes of coatings.

Emphysema	Abnormal distention of an organ or a part of the body, especially the lungs, with air or other gas.
Endocrine	Of or pertaining to an endocrine gland or its secretion; an internal secretion; hormone.
Energetics	The branch of physics that deals with energy.
Enzyme	Any of a group of catalytic proteins that are produced by living cells and that mediate and promote the chemical processes of life without themselves being altered or destroyed.
Enzymology	The science that deals with the chemistry, biochemistry and biology of enzymes.
Ester	Any of a class of compounds that on hydrolysis yield an organic or inorganic acid and an alcohol or phenol.
Esterification	Conversion into an ester (as by the reaction of a carbolic acid with an alcohol).
Ethical drugs	Drugs sold only upon medical prescription.
Eukaryote	A cell or organism with membrane-bound, structurally discrete nuclei and well-developed cell organelles. Eukaryotes include all organisms except viruses, bacteria, and blue-green algae. (Compare prokaryote.)
Factor VIII	Used in the treatment of hemophiliacs; essential for blood clotting.
Fatty acids	Any of the saturated or unsaturated mono-carboxylic acids that occur naturally in the form of glycerides in fats and fatty oils.
Fermentation	An anaerobic bioprocess. Fermentation is used in various industrial processes for the manufacture of products such as alcohols, acids, and cheese by the action of yeasts, molds, and bacteria.
Fibrinolysis	The breakdown of fibrin to soluble products usually through enzymatic action.

Fine chemical	A chemical (as a photographic chemical, a perfume, or a pharmaceutical) produced and handled in relatively small amounts and usually in a more or less pure state.
Follicle stimulating	Fertility hormone. (FSH) hormone
Gene expression	The mechanism whereby the genetic directions in any particular cell are decoded and processed into the final functioning product, usually a protein.
Genetic engineering	A technology used at the laboratory level to alter the hereditary apparatus of a living cell so that the cell can produce more or different chemicals, or perform completely new functions. These altered cells are then used in industrial production. Genetic engineering transfer techniques include cell fusion (protoplast fusion, hybridoma), incubation of cells with a calcium phosphate precipitate of DNA fragments, direct intracellular nuclear injection of DNA fragments, or transformation of cells with modified vectors (recombinant DNA).
Genetics	The science of heredity, dealing with resemblances and differences of related organisms resulting from the interaction of their genes and the environment.
Gene transfer	The use of genetic or physical manipulation to introduce foreign genes into host cells to achieve desired characteristics in progeny.
Glucosidase	An enzyme that hydrolyzes a glucoside.
Hirudin	Anti-coagulant.
Homogenates	Biologic tissue that has been finely divided (as by a grinder) and thoroughly mixed.
Hormone	A chemical messenger found in the circulation of higher organisms that transmits regulatory messages to cells.
Host-vector system	Compatible combinations of host (e.g., bacterium) and vector (e.g., plasmid) that allow stable introduction of foreign DNA into cells.
Human growth hormone (hGH)	Used in the treatment of dwarfism. Potentially could improve wound healing and treat osteoporosis.

Human insulin	Hormone that stimulates cell growth via glucose uptake by cells. Insulin deficiency leads to diabetes.
Hyaluronic acid	A viscous mucopolysaccharide acid that occurs chiefly in connective tissues or their derivatives.
Hybridization	Refers to the noncovalent binding of parts or all of DNA or RNA strands to each other or themselves due to complementarity regions of paired bases.
Hybridoma	Product of fusion between myeloma cell (which divides continuously in culture and is"immortal") and lymphocyte antibody-producing cell); the resulting cellgrows in culture and produces monoclonal antibodies.
Hydroxylation	Chemical reaction involving addition of hydroxyl (-OH) group to chemical compound.
Hypertensive	Characterized by a rise in blood pressure.
Immobilized cell	Techniques used for the fixation of cells or enzymes onto solid supports. Immobilized cells and enzymes are used in continuous bioprocessing.
Immobilized enzyme	Techniques used for the fixation of enzymes or cells onto solid supports. Immobilized cells and enzymes are used in continuous bioprocessing.
Immunology	The branch of medicine dealing with immunity from disease and the production of such immunity.
Infrastructure	Foundation, groundwork.
Inoculant	Substance used to make an inoculation.
Instrumentation	A branch of science concerned with the development, manufacture, and utilization of instruments.
Interferons	A class of glycoproteins (proteins with sugar groups attached at specific locations) important in immune function and thought to inhibit viral infections.
Interleukin-2 (IL-2)	Used in treatment of immune patients: AIDS, cancer, pre-operative, surgical patients, etc.

In vitro	Literally, in glass; pertaining to a biological reaction taking place in an artificial apparatus; sometimes used to include the growth of cells from multicellular organisms under cell culture conditions. In vitro diagnostic products are products used to diagnose disease outside of the body after a sample has been taken from the body.
Joint venture	Form of association of separate business entities which falls short of a formal merger but united certain agreed on resources of each entity for a limited purpose; in practice most joint ventures are partnerships.
Kreutzfeld-Jakob	A rare, fatal brain disorder. It is a Disease progressive dementia wich usually results in death within one year.
LSH	Lutenising hormone (used in the diagnosis and treatment of sub-fertile couples).
Mastitis	Inflammation of the breast or udder, usually caused by infection.
Metabolite	A product of metabolism.
Metabolism	The physical and chemical processes by which foodstuffs are synthesized into complex elements, complex substances are transformed into simple ones, and energy is made available for use by an organism.
Metastasis	The transference of disease-producing organisms to other parts of the body by way of blood vessels, lymphatics or membranous surfaces.
Methane	A colorless, odorless, flammable gas, the main constituent of marsh gas and the firedamp of coal mines, obtained commercially from natural gas: the first member of the methane, or alkane, series of hydrocarbons.
Microbe	A very minute organism.
Microbial	Being of or between microbes; done by or by the use of microbes; developed from microbes.
Microbiology	The science dealing with the structure, function, uses, etc., of microscopic organisms.

Molecular biology	A branch of biology dealing with the ultimate physicochemical organization of living matter.
Monoclonal antibodies	(MAbs) Homogeneous antibodies derived from a single clone of cells; MAbs recognize only one chemical structure. MAbs are useful in a variety of industrial and medical capacities since they are easily produced in large quantities and have remarkable specificity.
Morphogenesis	The development of life from preexisting life.
Neuroscience	The study of the brain and nerve tissue.
Nucleic acids	Macromolecules composed of sequences of nucleotide bases. There are two kinds of nucleic acids: DNA, which contains the sugar deoxyribose, and RNA, which contains the sugar ribose.
Nucleotide base	A structural unit of nucleic acid. The bases present in DNA are adenine, cytosine, guanine, and thymine. In RNA, uracil substitutes for thymine.
Oligosaccharides	Any of the saccharides (sugars) that contain a known small number of constituent monosaccharide units and include especially the disaccharides, trisaccharides and tetrasaccharides.
Oncology	The study of tumors.
Oxidation	Combination with oxygen or with more oxygen.
Oxytocin	A hormone secreted by the pituitary gland.
Parasitology	A branch of biology dealing with parasites and parasitism especially among animals.
Patent	A limited property right granted to inventors by government allowing the inventor of a new invention the right to exclude all others from making, using, or selling the invention unless specifically approved by the inventor, for a specified time period in return for full disclosure by the inventor about the invention.

Pathology	The study of abnormality, especially the study of diseases, their essential nature, causes, and development, and the structural and functional changes produced by them.
Peptide	A linear polymer of amino acids. A polymer of numerous amino acids is called a polypeptide. Polypeptides may be grouped by function, such as "neuroactive" polypeptides.
Perinatal	Occuring at about the time of birth.
Phage	A learned borrowing from Greek meaning "eating," "devouring," used in biology to refer to phagocytes (a blood cell that ingests and destroys foreign particles, bacteria, and other cells.
Pharmaceuticals	Products intended for use in humans, as well as in vitro applications to humans, including drugs, vaccines, diagnostics, and biological response modifiers.
Phytotechnology	Plant technology.
Plasmin	A proteolytic enzyme that dissovles the fibrin of blood clots and that is formed by the activation of plasminogen.
Plasminogen	The precursor of plasmin found in blood plasma and serum.
Prokaryote	A cell or organism lacking membrane-bound, structurally discreet nuclei and organelles. Prokaryotes include bacteria and the blue-green algae. (Compare eukaryote.)
Prophylactics	Preventing or contributing to the prevention of disease.
Protease	Any enzyme that acts upon proteins.
Protein	A polypeptide consisting of amino acids. In their biologically active states, proteins function as catalysts in metabolism and, to some extent, as structural elements of cells and tissues.
Protein A	Used in the plasmaphoresis of cancer patients.
Pyrethrin	A viscous, water-insoluble liquid extracted from pyrethrum flower (ex: crysanthemum) used as an insecticide.

Radiobiology	A branch of biology dealing with the interaction of biological systems and radiant energy or radioactive materials.
Reagent	A substance that takes part in a chemical reaction.
rDNA	Recombinant DNA. The hybrid DNA produced by joining pieces of DNA from different organisms together in vitro.
Recombination	Formation of a new association of genes or DNA sequences from different parental origins.
Rennin	A coagulating enzyme forming the active principle of rennet and able to curdle milk.
Replication	The synthesis of new DNA from existing DNA and the formation of new cells by cell division.
Restriction enzymes	Bacterial enzymes that cut DNA at specific DNA sequences.
Ribosome	Any of several minute particles composed of protein and RNA and found in the cytoplasm of a cell.
RNA	Ribonucleic acid; any of the class of nucleic acids that contains ribose, found chiefly in the cytoplasm of cells.
Ricin	An amorphous and violently poisonous protein in the castor bean.
Scale-up	The transition of a process from an experimental scale to an industrial scale.
Serum	The watery portion of an animal fluid remaining after coagulation. Blood serum: immune blood serum that contains specific immune bodies (as antitoxins or agglutinins).
Somatic cell	One of the cells composing parts of the body (e.g., tissues, organs) other than a germ cell.
Startup financing	Financing usually supplied by venture capitalist to fund the early R&D, production, sale of a new company's products.
Steroid	Any of a class of compounds containing the carbon ring system of the sterols and including the sterols, certain hormones and glycosides, etc.

Strain	A group of organisms of the same species having distinctive characteristics but not usually considered a separate breed or variety. A genetically homogenous population of organisms at a subspecies level that can be differentiated by a biochemical, pathogenic, or other taxonomic feature.
Technology transfer	The movement of technical information and/or materials, used for producing a product or process, from one sector to another; most often refers to flow of information between public and private sectors or between countries.
Thaumatin	A natural, sweet protein.
Thrombin	The substance or agent that causes the coagulation of blood.
Tissue culture	Refers to processes and apparatus which permit the growth and maintenance of cell lines. Used in the production of vaccines, steroids, antibodies and skin and organ transplant materials.
TNF	Tumor necrosis factor. Used in treatment of tumors.
TPA	Tissue plasminogen activator. Blood clot dissolving agent for use in heart attacks and deep vein thrombosis.
Toxicology	A science that deals with poisons and their effect on living organisms, with substances otherwise harmless that prove toxic under particular conditions, and with the clinical, industrial, legal, or other problems involved.
Vaccine	A suspension of attenuated or killed bacteria or viruses, or portions thereof, injected to produce active immunity.
VAT	Value Added Tax.
Vector	DNA molecule used to introduce foreign DNA into host cells. Vectors include plasmids, bacteriophages (virus), and other forms of DNA. A vector must be capable of replicating autonomously and must have cloning sites for the introduction of foreign DNA.

Venture capital	Venture capital funds. Money that is invested in companies with which a high level of risk is associated.
Virology	A branch of science that deals with viruses.
Virus	An infectious agent, especially any of a group of ultramicroscopic, infectious agents that reproduce only in living cells.
Yeast	A fungus of the family Saccharomycetacea that is used especially in the making of alcoholic liquors and as leavening in baking. Yeast are also commonly used in bioprocesses.

• U.S. GOVERNMENT PRINTING OFFICE 1987—181-876 60085